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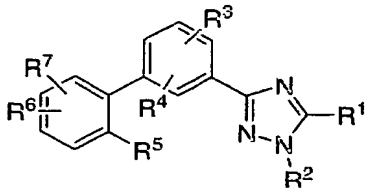
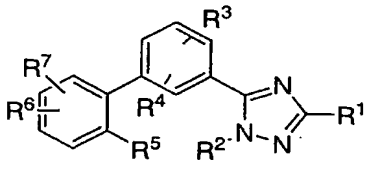
(54) Title: BIARYL SUBSTITUTED TRIAZOLES AS SODIUM CHANNEL BLOCKERS



(I)



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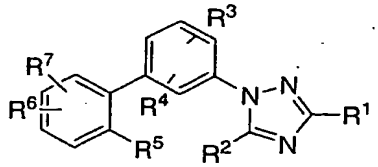

(III)

(57) Abstract: Biaryl substituted triazole compounds represented by Formula (I), (II) or (III), or pharmaceutically acceptable salts thereof, and a process for making such compounds and salts thereof. Pharmaceutical compositions comprise an effective amount of the instant compounds, either alone, or in combination with one or more other therapeutically active compounds, and a pharmaceutically acceptable carrier. Methods of treating conditions associated with, or caused by, sodium channel activity, including, for example, acute pain, chronic pain, visceral pain, inflammatory pain, neuropathic pain, epilepsy, irritable bowel syndrome, depression, anxiety, multiple sclerosis, and bipolar disorder, comprise administering an effective amount of the present compounds, either alone, or in combination with one or more other therapeutically active compounds. A method of administering local anesthesia comprises administering an effective amount of a compound of the instant invention, either alone, or in combination with one or more other therapeutically active compounds, and a pharmaceutically acceptable carrier.

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TITLE OF THE INVENTION

BIARYL SUBSTITUTED TRIAZOLES AS SODIUM CHANNEL BLOCKERS

FIELD OF THE INVENTION

The present invention is directed to a series of biaryl substituted triazole compounds. In particular, this invention is directed to biaryl substituted triazoles that are sodium channel blockers useful for the treatment of chronic and neuropathic pain. The compounds of the present invention are also useful for the treatment of other conditions, including disorders of the central nervous system (CNS) such as epilepsy, manic depression, bipolar disorder, depression, anxiety and diabetic neuropathy.

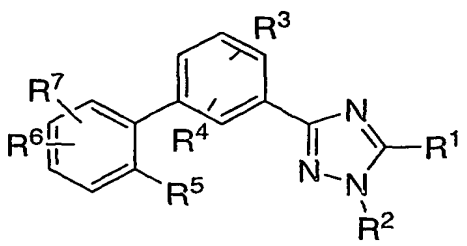
SUMMARY OF THE INVENTION

The present invention is directed to biaryl substituted triazole compounds which are sodium channel blockers useful for the treatment of chronic and neuropathic pain. The compounds of the present invention are also useful for the treatment of other conditions, including disorders of the CNS such as epilepsy, depression, anxiety, manic depression and bipolar disorder. This invention also provides pharmaceutical compositions comprising a compound of the present invention, either alone, or in combination with one or more therapeutically active compounds, and a pharmaceutically acceptable carrier.

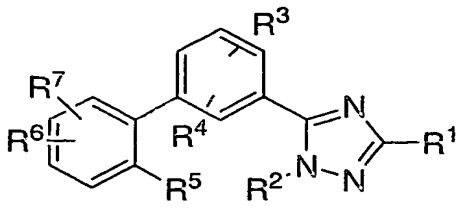
This invention further comprises methods for the treatment of acute pain, chronic pain, visceral pain, inflammatory pain, neuropathic pain and disorders of the CNS including, but not limited to, epilepsy, depression, anxiety, manic depression and bipolar disorder comprising administering the compounds and pharmaceutical compositions of the present invention. The invention also encompasses a process for making the instant compounds.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises compounds represented by Formula (I) or (II):



(I)



(II)

or pharmaceutically acceptable salts thereof, wherein

R^1 is

(a) H;

(b) C_1-C_6-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl,C_3-C_6-cycloalkyl, or C_1-C_4-alkyl-[C_3-C_6-cycloalkyl], any of which is optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, O-$CONR^aR^b$, NR^aR^b, $N(R^a)CONR^aR^b$, COO-(C_1-C_4)alkyl, COOH, CN, $CONR^aR^b$;

(c) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl;

(d) NR^aR^b, $-N(COR^a)R^b$, $-N(SO_2R^a)R^b$, $-N(R^a)CON(R^a)_2$, $-N(R^a)SO_2R^a$, $-N(OR^a)CONR^aR^b$, or -$N(R^a)SO_2N(R^a)_2$;

(e) $-CH(OR^a)R^a$, $-C(OR^b)CF_3$, $-CH(NHR^b)R^a$, $-C(=O)R^a$, $C(=O)CF_3$, $-SOCH_3$, $-SO_2CH_3$, $COOR^a$, CN, $CONR^aR^b$, $-COCONR^aR^b$, $-SO_2NR^aR^b$, $-CH_2O-SO_2NR^aR^b$, $SO_2N(R^a)OR^a$, $-C(=NH)NH_2$, $-CR^a=N-OR^a$, $CH=CHCONR^aR^b$;

(f) $-CONR^a(CH_2)_{0-2}C(R^a)(R^b)(CH_2)_{0-2}CONR^aR^b$;

(g) $-C(R^a)=C(R^b)-COOR^a$, or $-C(R^a)=C(R^b)-CONR^aR^b$;

R^a is

(a) H;

(b) C_1-C_4-alkyl, optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, $S(O)_{0-2}$-(C_1-C_4)alkyl, $-OCONH_2$, $-OCONH(C_1$-C_4alkyl), $-OCON(C_1$-C_4alkyl)(C_1-C_4alkyl), $-OCONHC_1$-C_4alkyl-aryl), $-OCON(C_1$-C_4alkyl)(C_1-C_4alkyl-aryl), NH_2, $NH(C_1$-C_4alkyl), $N(C_1$-C_4alkyl)(C_1-C_4alkyl), $NH(C_1$-C_4alkyl-aryl), $N(C_1$-C_4alkyl)(C_1-C_4alkyl-aryl), $NHCONH_2$, $NHCONH(C_1$-C_4alkyl), $NHCONH(C_1$-C_4alkyl-aryl), $-NHCON(C_1$-C_4alkyl)(C_1-C_4alkyl), $NHCON(C_1$-C_4alkyl)(C_1-C_4alkyl-aryl), $N(C_1$-C_4alkyl)$CON(C_1$-C_4alkyl)(C_1-C_4alkyl), N(C_1-

C_4alkyl)CON(C_1-C_4alkyl)(C_1-C_4alkyl-aryl), COO-(C_1-C_4-alkyl), COOH, CN, $CONH_2$, CONH(C_1-C_4alkyl), CON(C_1-C_4alkyl)(C_1-C_4alkyl);

(c) C_0-C_4-alkyl-(C_1-C_4)-perfluoroalkyl; or

(d) -C_1-C_4-alkyl-aryl, wherein aryl is phenyl, pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, triazolyl, pyrazolyl, thiazolyl, isoxazolyl, oxazolyl, or oxadiazolyl, any aryl of which is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) -NO_2, iv) –C(=O)(C_1-C_4alkyl), v) -O(C_1-C_4alkyl), vi) -N(C_1-C_4alkyl)(C_1-C_4alkyl), xiii) -C_{1-10}alkyl, and xiv) -C_{1-10}alkyl,wherein one or more of the alkyl carbons can be replaced by a - O-, -$S(O)_{1-2}$-, -O-C(O)-, -C(O)-O-, -C(O)-, -CH(OH)-, -C=C-, or -C≡C-;

R^b is

(a) H; or

(b) C_1-C_6-alkyl, optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, $S(O)_{0-2}$-(C_1-C_4)alkyl, -$OCONH_2$, -OCONH(C_1-C_4alkyl), NH_2, NH(C_1-C_4alkyl), N(C_1-C_4alkyl)(C_1-C_4alkyl), $NHCONH_2$, NHCONH(C_1-C_4alkyl), -NHCON(C_1-C_4alkyl)(C_1-C_4alkyl), COO-(C_1-C_4-alkyl), COOH, CN, or $CONH_2$;

R^2 is:

(a) H;

(b) -C_1-C_4-alkyl, -C_3-C_6-cycloalkyl or -C_1-C_4-alkyl-(C_3-C_6)-cycloalkyl, optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, $S(O)_{0-2}$-(C_1-C_4)alkyl, O-$CONR^aR^b$, NR^aR^b, N(R^a)$CONR^aR^b$, COO-(C_1-C_4)alkyl, COOH, CN, $CONR^aR^b$;

(c) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl;

(d) -C(=O)(R^a), -$CONR^aR^b$, -COO-(C_1-C_4)alkyl, - SO_2R^a, -$SO_2N(R^a)(R^b)$;

R^3 and R^4 each independently is:

(a) H;

(b) -C_1-C_6-alkyl, -C_2-C_6-alkenyl, or -C_2-C_6-alkynyl or -C_3-C_6-cycloalkyl, any of which is optionally substituted with one or more of the following substituents: F, CF_3, -O-(C_1-C_4)alkyl, CN, -N(R^a)(R^b), -N(R^a)CO-(C_1-C_4)alkyl, $COOR^b$, CON(R^a)(R^b) or phenyl;

(c) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, or -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl; or

(d) CN, NH_2, NO_2, F, Cl, Br, I, OH, OCON(R^a)(R^b) O(C_1-C_4-alkyl)$CONR^aR^b$, -$OSO_2N(R^a)(R^b)$, $COOR^b$, CON(R^a)(R^b), or aryl, wherein aryl is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) -NO_2, iv) –C(=O)(R^a), v) -OR^a, vi) -NR^aR^b, vii) -C_{0-4}alkyl-CO-OR^a, viii) -(C_0-

4alkyl)-NH-CO-OR^a, ix) -(C_{0-4}alkyl)-CO-N(R^a)(R^b), x) -$S(O)_{0-2}R^a$, xi) -$SO_2N(R^a)(R^b)$, xii) -$NR^aSO_2R^a$, xiii) -C_{1-10}alkyl, and xiv) -C_{1-10}alkyl,wherein one or more of the alkyl carbons can be replaced by a -NR^a-, - O-, -$S(O)_{1-2}$-, -O-C(O)-, -C(O)-O-, -C(O)-N(R^a)-, -N(R^a)-C(O)-, -N(R^a)-C(O)-N(R^a)-, -C(O)-, -CH(OH)-, -C=C-, or -C≡C; and

R^5, R^6 and R^7 each independently is:

(a) H;

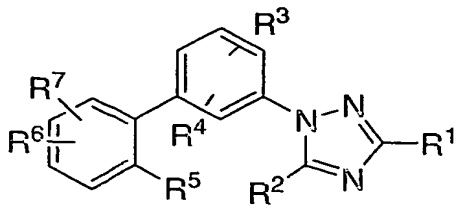
(b) C_1-C_6-alkyl, C_2-C_4-alkenyl, or C_2-C_4-alkynyl or C_3-C_6-cycloalkyl, any of which is optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, OCON(R^a)(R^b), NR^aR^b, $COOR^a$, CN, $CONR^aR^b$, $N(R^aR^b)CONR^aR^b$;

(c) -O- C_1-C_6-alkyl, or -O-C_3-C_6-cycloalkyl, -S-C_1-C_6-alkyl or -S-C_3-C_6-cycloalkyl, any of which is optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, NH_2, NH(C_1-C_4-alkyl), N(C_1-C_4-alkyl)$_2$, COOH , CN, $CONH_2$, CONH(C_1-C_4-alkyl), CONH(C_1-C_4-alkyl)$_2$, SO_2NH_2, $SO_2NH(C_1$-C_4-alkyl), tetrazolyl, triazolyl, imidazolyl, oxazolyl, oxadiazolyl, isooxazolyl, thiazolyl, furyl, thienyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyrazinyl, phenyl, piperidinyl, morpholinyl, pyrrolidinyl, or piperazinyl;

(d) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, or -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl;

(e) CN, N(R^a)(R^b), NO_2, F, Cl, Br, I, -OR^a, -SR^a, -OCON(R^a)(R^b), -$OSO_2N(R^a)(R^b)$, $COOR^b$, CON(R^a)(R^b), -N(R^a)CON(R^a)(R^b), -N(R^a)$SO_2N(R^a)(R^b)$, -C(OR^b)R^a, -C(OR^a)CF_3, -C(NHR^a)CF_3, -C(=O)R^a, C(=O)CF_3, -$SOCH_3$, -SO_2CH_3, -$NHSO_2$(C_{1-6}-alkyl), -$NHSO_2$-aryl, $SO_2N(R^a)(R^b)$, -$CH_2OSO_2N(R^a)(R^b)$, $SO_2N(R^b)$-OR^a, -C(=NH)NH_2, -CR_a=N-OR_a, CH=CH or aryl, wherein aryl is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) -NO_2, iv) –C(=O)(R^a), v) -OR^a, vi) -NR^aR^b, vii) -C_{0-4}alkyl-CO-OR^a, viii) -(C_{0-4}alkyl)-NH-CO-OR^a, ix) -(C_{0-4}alkyl)-CO-N(R^a)(R^b), x) -$S(O)_{0-2}R^a$, xi) -$SO_2N(R^a)(R^b)$, xii) -$NR^aSO_2R^a$, xiii) -C_{1-10}alkyl, and xiv) -C_{1-10}alkyl, wherein one or more of the alkyl carbons can be replaced by a -NR^a-, - O-, -$S(O)_{1-2}$-, -O-C(O)-, -C(O)-O-, -C(O)-N(R^a)-, -N(R^a)-C(O)-, -N(R^a)-C(O)-N(R^a)-, -C(O)-, -CH(OH)-, -C=C-, or -C≡C.

The present invention further comprises compounds described by Formula III:



III

or pharmaceutical salts thereof, wherein
$R^1 - R^7$ each is as defined above.

In a first aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein
R^5 is other than H, and all other variables are as previously defined.

In an embodiment of this first aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein
R^5 is $-OR^a$, and all other variables are as previously defined.

In another embodiment of this first aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein
R^1 is optionally substituted C_1-C_6-alkyl, optionally substituted C_3-C_6-cycloalkyl, $-C(=O)R^a$ or $CONR^aR^b$, and all other variables are as previously defined.

In a second aspect, the present invention provides a compound described by the chemical Formula (II), or a pharmaceutically acceptable salt thereof, wherein
R^5 is other than H, and all other variables are as previously defined.

In an embodiment of this second aspect, the present invention provides a compound described by the chemical Formula (II), or a pharmaceutically acceptable salt thereof, wherein
R^5 is $-OR^a$, and all other variables are as previously defined.

In another embodiment of this second aspect, the present invention provides a compound described by the chemical Formula (II), or a pharmaceutically acceptable salt thereof, wherein

R^1 is optionally substituted C_1-C_6-alkyl, optionally substituted C_3-C_6-cycloalkyl, -$C(=O)R^a$ or $CONR^aR^b$, and all other variables are as previously defined.

In a third aspect, the present invention provides a compound described by the chemical Formula (III), or a pharmaceutically acceptable salt thereof, wherein

R^5 is other than H, and all other variables are as previously defined.

In an embodiment of this third aspect, the present invention provides a compound described by the chemical Formula (III), or a pharmaceutically acceptable salt thereof, wherein

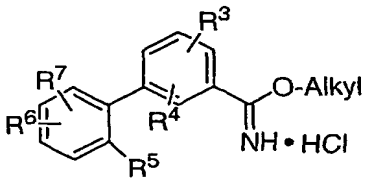
R^5 is $-OR^a$, and all other variables are as previously defined.

In another embodiment of this third aspect, the present invention provides a compound described by the chemical Formula (III), or a pharmaceutically acceptable salt thereof, wherein

R^1 is optionally substituted C_1-C_6-alkyl, optionally substituted C_3-C_6-cycloalkyl, -$C(=O)R^a$ or $CONR^aR^b$, and all other variables are as previously defined.

The present invention further provides a process for making a compound of Formula (I), or a pharmaceutically acceptable salt thereof,

the process comprising reacting a compound of Formula **34** or **35**:



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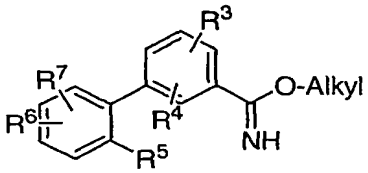

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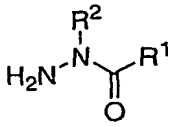
with a compound of Formula **36**:



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wherein $R^1 - R^7$ each is as defined above, in the presence of a base to yield a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In a first aspect of the inventive process, the present invention provides a process for making a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, $-C(=O)R^a$, $COOR^a$, $CONR^aR^b$, C_1-C_6 alkyl or C_3-C_6 cycloalkyl, wherein said alkyl and cycloalkyl is optionally substituted with one or more of F, OH, or NR^aR^b,

R^2 is H,

R^5, R^6 and R^7 each independently is H, F, $-OR^a$, C_1-C_6-alkyl, or $-O-C_1$-C_6-alkyl, wherein said alkyl is optionally substituted with one or more of F, CF_3, or O-(C_1-C_4)alkyl, and all other variables are as previously defined.

In a second aspect of the inventive process, the present invention provides a process for making a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein

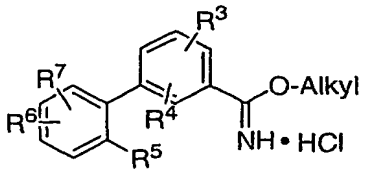
the base is a metal acetate, metal carbonate or tertiary amine.

In a third aspect of the inventive process, the present invention provides a process for making a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein

the base is potassium acetate.

The present invention further provides a process for making a compound of Formula (I), or a pharmaceutically acceptable salt thereof,

the process comprising reacting a compound of Formula **34** or **35**:



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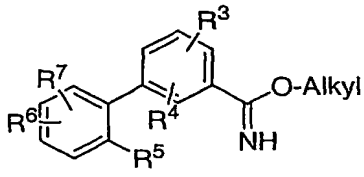
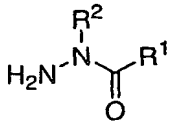


35

with a compound of Formula **36**:



36

wherein $R^1 - R^7$ each is as defined above, in the presence of a base, and optionally an alcoholic solvent, and optionally heat, to yield a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, and alkynyl means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, and heptyl. "Alkenyl," "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, and 1,2,3,4-tetrahydronaphalene.

The term "aryl" includes, but is not limited to, an aromatic substituent that is a single ring or multiple rings fused together. When formed of multiple rings, at least one of the constituent rings is aromatic. The term "aryl", unless specifically noted otherwise, also includes heteroaryls, and thus includes stable 5- to 7-membered monocyclic and stable 9- to 10-membered fused bicyclic heterocyclic ring systems that consist of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. Suitable aryl groups include phenyl, naphthyl, pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, triazolyl, pyrazolyl, thiazolyl, isoxazolyl, oxazolyl, and oxadiazolyl

The term "cycloalkyloxy," unless specifically stated otherwise, includes a cycloalkyl group connected by a short C_{1-2}alkyl to the oxy connecting atom.

The term "C_{0-6}alkyl" includes alkyls containing 6, 5, 4, 3, 2, 1, or no carbon atoms. An alkyl with no carbon atoms is a hydrogen atom substituent when the alkyl is a terminal group and is a direct bond when the alkyl is a bridging group.

The term "amine," unless specifically stated otherwise, includes primary, secondary and tertiary amines.

The term "carbonyl," unless specifically stated otherwise, includes a C_{0-6}alkyl substituent group when the carbonyl is terminal.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring. Further, optionally substituted multiple moieties such as, for example, alkylaryl are intended to mean that the alkyl and the aryl groups are optionally substituted. If only one of the multiple moieties is optionally substituted then it will be specifically recited such as "an alkylaryl, the aryl optionally substituted with halogen or hydroxyl."

Compounds described herein may contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers unless specifically stated otherwise.

Compounds described herein can contain one or more asymmetric centers and may thus give rise to diastereoisomers and optical isomers. The present invention includes all such possible diastereoisomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above chemical Formulas are shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of the chemical Formulas and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N, N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and tromethamine.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I, II or III (or a pharmaceutically acceptable salt thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. Such additional therapeutic agents can include, for example, i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists, iv) sodium channel antagonists, v) NMDA receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) NK1 antagonists, viii) non-steroidal anti-inflammatory drugs ("NSAID"), ix) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), x) tricyclic antidepressant drugs, xi) norepinephrine modulators, xii) lithium, xiii) valproate, and xiv) neurontin (gabapentin). The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

The present compounds and compositions are useful for the treatment of chronic, visceral, inflammatory and neuropathic pain syndromes. They are useful for the treatment of pain resulting from traumatic nerve injury, nerve compression or entrapment, postherpetic neuralgia, trigeminal neuralgia, and diabetic neuropathy. The present compounds and compositions are also useful for the treatment of chronic lower back pain, phantom limb pain, chronic pelvic pain, neuroma pain, complex regional pain syndrome, chronic arthritic pain and related neuralgias, and pain associated with cancer, chemotherapy, HIV and HIV treatment-induced neuropathy. Compounds of this invention may also be utilized as local anesthetics. Compounds of this invention are useful for the treatment of irritable bowel syndrome and related disorders, as well as Crohns disease.

The instant compounds have clinical uses for the treatment of epilepsy and partial and generalized tonic seizures. They are also useful for neuroprotection under ischaemic conditions caused by stroke or neural trauma and for treating multiple sclerosis. The present compounds are useful for the treatment of depression, anxiety, bipolar disorder and tachy-arrhythmias.

Further, it is understood that compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions and disorders, as well as to prevent other conditions and disorders associated with sodium channel activity.

Creams, ointments, jellies, solutions, or suspensions containing the instant compounds can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.01mg/kg to about 140mg/kg of body weight per day are useful in the treatment of inflammatory and neuropathic pain, or alternatively about 0.5mg to about 7g per patient per day. For example, inflammatory pain may be effectively treated by the administration of from about 0.01mg to about 75mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Neuropathic pain may be effectively treated by the administration of from about 0.01mg to about 125mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 5.5g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 1000mg of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors. Such patient-related factors include the age, body weight, general health, sex, and diet of the patient. Other factors include the time and route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

In practice, the compounds represented by Formula I, II and III or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the

common dosage forms set out above, the compounds represented by Formula I, II and III or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I, II or III. The compounds of Formula I, II and III, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient. Thus, a tablet, cachet, or capsule conveniently contains 0.1mg, 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient taken one or two tablets, cachets, or capsules, once, twice, or three times daily.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage, andthus should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, and dusting powder. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I, II or III, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid, such as, for example, where the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, and preservatives (including anti-oxidants). Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, II or III, or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

The compounds and pharmaceutical compositions of this invention have been found to block sodium channels. Accordingly, an aspect of the invention is the treatment in mammals of maladies

that are amenable to amelioration through blockage of neuronal sodium channels, including, for example, acute pain, chronic pain, visceral pain, inflammatory pain, and neuropathic pain by administering an effective amount of a compound of this invention. The term "mammals" includes humans, as well as other animals, such as, for example, dogs, cats, horses, pigs, and cattle. Accordingly, it is understood that the treatment of mammals other than humans refers to the treatment of clinical conditions in non-human mammals that correlate to the above-recited conditions.

As used herein for purposes of the inventive process, the term "base" includes metal acetate bases, metal carbonate bases, and tertiary amine bases. Examples of metal acetate bases include potassium acetate and sodium acetate. Examples of metal carbonate bases include potassium carbonate and sodium carbonate. Tertiary amine bases include trialkyl amine bases such as triethylamine.

As used herein for purposes of the inventive process, the term "alcoholic solvent" or "alcohol solvent" includes, for example, methanol, ethanol, isopropanol and 1-butanol.

Where the inventive process utilizes heat, the process can be carried out in the temperature range of between about 40°C to about 150°C, including about 50°C to about 140°C, about 50°C to about 130°C, about 60°C to about 120°C, about 65°C to about 100°C, or about 65°C to about 85°C.

As used herein, the term "solvent/co-solvent mixture" includes solvent mixtures such as toluene/tetrahydrofuran, tetrahydrofuran/diethylether, toluene/diethylether, tetrahydrofuran/methyl-t-butylether, toluene/methyl-t-butylether, toluene/dioxane, and tetrahydrofuran/dioxane.

The abbreviations used herein have the following meanings (abbreviations not shown here have their meanings as commonly used unless specifically stated otherwise): Ac (acetyl), AIBN (2,2'-azobis(isobutyronitrile)), BINAP (1,1'-bi-2-naphthol), Bn (benzyl), CAMP (cyclic adenosine-3',5'-monophosphate), DAST ((diethylamino)sulfur trifluoride), DEAD (diethyl azodicarboxylate), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DIBAL (diisobutylaluminum hydride), DMAP (4-(dimethylamino)pyridine), DMF (N,N-dimethylformamide), Dppf (1,1'-bis(diphenylphosphino)-ferrocene), EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), Et_3N (triethylamine), GST (glutathione transferase), HMDS (Hexamethyldisilazide), LDA (lithium diisopropylamide), m-CPBA (metachloroperbenzoic acid), MMPP (monoperoxyphthalic acid), MPPM (monoperoxyphthalic acid), Ms (methanesulfonyl; mesyl; or SO_2Me), MsO (methanesulfonate or mesylate), NBS (N-bromo succinimide), NSAID (non-steroidal anti-inflammatory drug), o-Tol (ortho-tolyl), OXONE® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$), PCC (pyridinium chlorochromate), $Pd_2(dba)_3$ (Bis(dibenzylideneacetone) palladium(0)), PDC (pyridinium dichromate), PDE (Phosphodiesterase), Ph (Phenyl), Phe (Benzenediyl), PMB (para-methoxybenzyl), Pye (Pyridinediyl), r.t. or RT (room temperature), Rac (Racemic), SAM (aminosulfonyl; sulfonamide or SO_2NH_2), SEM (2-(trimethylsilyl)ethoxymethoxy), SPA (scintillation

proximity assay), TBAF (tetra-n-butylammonium fluoride), Th (2- or 3-thienyl), TFA (trifluoroacetic acid), TFAA (trifluoroacetic acid anhydride), THF (Tetrahydrofuran), Thi (Thiophenediyl), TLC (thin layer chromatography), TMS-CN (trimethylsilyl cyanide), TMSI (trimethylsilyl iodide), Tz (1H (or 2H)-tetrazol-5-yl), XANTPHOS (4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene), C_3H_5 (Allyl), Me (methyl), Et (ethyl), *n*-Pr (normal propyl), *i*-Pr (isopropyl), *n*-Bu (normal butyl), *i*-Butyl (isobutyl), *s*-Bu (secondary butyl), *t*-Bu (tertiary butyl), c-Pr (cyclopropyl), c-Bu (cyclobutyl), c-Pen (cyclopentyl), c-Hex (cyclohexyl).

The following *in vitro* and *in vivo* assays were used in assessing the biological activity of the instant compounds.

Compound Evaluation (*in vitro* assay):

The identification of inhibitors of the sodium channel is based on the ability of sodium channels to cause cell depolarization when sodium ions permeate through agonist-modified channels. In the absence of inhibitors, exposure of an agonist-modified channel to sodium ions will cause cell depolarization. Sodium channel inhibitors will prevent cell depolarization caused by sodium ion movement through agonist-modified sodium channels. Changes in membrane potential can be determined with voltage-sensitive fluorescence resonance energy transfer (FRET) dye pairs that use two components, a donor coumarin (CC_2DMPE) and an acceptor oxanol ($DiSBAC_2(3)$). Oxanol is a lipophilic anion and distributes across the membrane according to membrane potential. In the presence of a sodium channel agonist, but in the absence of sodium, the inside of the cell is negative with respect to the outside, oxanol is accumulated at the outer leaflet of the membrane and excitation of coumarin will cause FRET to occur. Addition of sodium will cause membrane depolarization leading to redistribution of oxanol to the inside of the cell, and, as a consequence, to a decrease in FRET. Thus, the ratio change (donor/acceptor) increases after membrane depolarization. In the presence of a sodium channel inhibitor, cell depolarization will not occur, and therefore the distribution of oxanol and FRET will remain unchanged.

Cells stably transfected with the PN1 sodium channel (HEK-PN1) were grown in polylysine-coated 96-well plates at a density of ca. 140,000 cells/well. The media was aspirated, and the cells were washed with PBS buffer, and incubated with 100µL of 10µM CC_2-DMPE in 0.02% pluronic acid. After incubation at 25°C for 45min, media was removed and cells were washed 2x with buffer. Cells were incubated with 100µL of $DiSBAC_2(3)$ in TMA buffer containing 20µM veratridine, 20nM brevetoxin-3, and test sample. After incubation at 25°C for 45min in the dark, plates were placed in the VIPR instrument, and the fluorescence emission of both CC_2-DMPE and $DiSBAC_2(3)$ recorded for 10s. At this point, 100µL of saline buffer was added to the wells to determine the extent of sodium-dependent

cell depolarization, and the fluorescence emission of both dyes recorded for an additional 20s. The ratio CC_2-DMPE/DiSBAC_2(3), before addition of saline buffer equals 1. In the absence of inhibitors, the ratio after addition of saline buffer is > 1.5. When the sodium channel has been completely inhibited by either a known standard or test compound, this ratio remains at 1. It is possible, therefore, to titrate the activity of a sodium channel inhibitor by monitoring the concentration-dependent change in fluorescence ratio.

Electrophysiological Assays (*In Vitro* assays):

Cell preparation: A HEK-293 cell line stably expressing the PN1 sodium channel subtype was established in-house. The cells were cultured in MEM growth media (Gibco) with 0.5mg/mL G418, 50 units/mL Pen/Strep and 1mL heat-inactivated fetal bovine serum at 37°C and 10% CO_2. For electrophysiological recordings, cells were plated on 35mm dishes coated with poly-D-lysine.

Whole-cell recordings: HEK-293 cells stably expressing the PN1 sodium channel subtype were examined by whole cell voltage clamp (Hamill, *et al.* Pfluegers Archives 391:85-100 (1981)) using an EPC-9 amplifier and Pulse software (HEKA Electronics, Lamprecht, Germany). Experiments were performed at room temperature. Electrodes were fire-polished to resistances of 2-4 MΩ. Voltage errors were minimized by series resistance compensation, and the capacitance artefact was canceled using the EPC-9's built-in circuitry. Data were acquired at 50 kHz and filtered at 7-10 kHz. The bath solution consisted of 40 mM NaCl, 120 mM NMDG Cl, 1 mM KCl, 2.7 mM $CaCl_2$, 0.5 mM $MgCl_2$, 10 mM NMDG HEPES, pH 7.4, and the internal (pipet) solution contained 110 mM Cs-methanesulfonate, 5 mM NaCl, 20mM CsCl, 10mM CsF, 10 mM BAPTA (tetra Cs salt), 10 mM Cs HEPES, pH 7.4.

The following protocols were used to estimate the steady-state affinity of compounds for the resting and inactivated state of the channel (K_r and K_i, respectively):

1. 8ms test-pulses to depolarizing voltages from –60mV to +50mV from a holding potential of –90mV were used to construct current-voltage relationships (IV-curves). A voltage near the peak of the IV-curve (typically –10 or 0 mV) was used as the test-pulse voltage throughout the remainder of the experiment.

2. Steady-state inactivation (availability) curves were constructed by measuring the current activated during an 8ms test-pulse following 10s conditioning pulses to potentials ranging from –120mV to –10mV.

3. Compounds were applied at a holding potential at which 20-50% of the channels was inactivated and sodium channel blockage was monitored during 8ms test pulses at 2s intervals.

4. After the compounds equilibrated, the voltage-dependence of steady-state inactivation in the presence of compound was determined according to protocol 2) above. Compounds

that block the resting state of the channel decrease the current elicited during test-pulses from all holding potentials, whereas compounds that primarily block the inactivated state shift the mid-point of the steady-state inactivation curve. The maximum current at negative holding potentials (I_{max}) and the difference in the mid-points of the steady-state inactivation curves (ΔV) in control and in the presence of a compound were used to calculate K_r and K_i using the following equations:

$$K_r = \frac{[Drug] * I_{Max,Drug}}{I_{Max,Control} - I_{Max,Drug}}$$

$$K_i = \frac{[Drug]}{\left(1 + \frac{[Drug]}{K_r}\right) * e^{\frac{-\Delta V}{k}} - 1}$$

In cases where the compound did not affect the resting state, K_i was calculated using the following equation:

$$K_i = \frac{[Drug]}{e^{\frac{-\Delta V}{k}} - 1}$$

Rat Formalin Paw test (*in vivo* assay):

Compounds were assessed for their ability to inhibit the behavioral response evoked by a 50µL injection of formalin (5%). A metal band was affixed to the left hind paw of male Sprague-Dawley rats (Charles River, 200-250g) and each rat was conditioned to the band for 60min within a plastic cylinder (15cm diameter). Rats were dosed with either vehicle or a test compound either before (local) or after (systemic) formalin challenge. For local administration, compounds were prepared in a 1:4:5 vehicle of ethanol, PEG400 and saline (EPEGS) and injected subcutaneously into the dorsal surface of the left hind paw 5min prior to formalin. For systemic administration, compounds were prepared in either a EPEGS vehicle or a Tween80 (10%)/sterile water (90%) vehicle and were injected i.v. (via the lateral tail vein 15min after formalin) or p.o. (60min before formalin). The number of flinches was counted continuously for 60min using an automated nociception analyzer (UCSD Anesthesiology Research, San Diego, CA). Statistical significance was determined by comparing the total flinches detected in the early (0-10min) and late (11-60min) phase with an unpaired t-test.

***In vivo* assay using Rat CFA model:**

Unilateral inflammation was induced with a 0.2 ml injection of complete Freund's adjuvant (CFA: Mycobacterium tuberculosis, Sigma; suspended in an oil/saline (1:1) emulsion; 0.5mg Mycobacterium/mL) in the plantar surface of the left hindpaw. This dose of CFA produced significant hind paw swelling but the animals exhibited normal grooming behavior and weight gain over the course of the experiment. Mechanical hyperalgesia was assessed 3 days after tissue injury using a Randall-Selitto test. Repeated Measures ANOVA, followed by Dunnett's Post Hoc test.

SNL: Mechanical Allodynia (*in vivo* assay):

Tactile allodynia was assessed with calibrated von Frey filaments using an up-down paradigm before and two weeks following nerve injury. Animals were placed in plastic cages with a wire mesh floor and allowed to acclimate for 15min before each test session. To determine the 50% response threshold, the von Frey filaments (over a range of intensities from 0.4 to 28.8g) were applied to the mid-plantar surface for 8s, or until a withdrawal response occurred. Following a positive response, an incrementally weaker stimulus was tested. If there was no response to a stimulus, then an incrementally stronger stimulus was presented. After the initial threshold crossing, this procedure was repeated for four stimulus presentations per animal per test session. Mechanical sensitivity was assessed 1 and 2 hr post oral administration of the test compound.

The compounds described in this invention displayed sodium channel blocking activity of less than about 0.05μM to less than about 50μM in the *in vitro* assays described above. It is advantageous that the compounds display sodium channel blocking activity of less than about 5μM in the *in vitro* assays. It is more advantageous that the compounds display sodium channel blocking activity of less than about 1μM in the *in vitro* assays. It is even more advantageous that the compounds display sodium channel blocking activity of less than about 0.1μM in the *in vitro* assays. It is still more advantageous that the compounds display sodium channel blocking activity of less than about 0.05μM in the *in vitro* assays.

The present compounds can be prepared according to the general Schemes provided below as well as the procedures provided in the Examples. The following Schemes and Examples further describe, but do not limit, the scope of the invention.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions: All operations were carried out at room or ambient temperature; that is, at a temperature in the range of 18-25°C. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000pascals: 4.5-30mm. Hg) with a bath temperature of up to 60°C. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only. Melting points are uncorrected and 'd' indicates decomposition. The melting points

given are those obtained for the materials prepared as described. Polymorphism may result in isolation of materials with different melting points in some preparations. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. When given, yields are for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300MHz, 400MHz or 500MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations are used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

Methods of Synthesis

Compounds of the present invention can be prepared according to the Schemes provided below as well as the procedures provided in the Examples. The substituents are the same as in the above Formulas except where defined otherwise or otherwise apparent to the ordinary skilled artisan.

The novel compounds of the present invention can be readily synthesized using techniques known to those skilled in the art, such as those described, for example, in Advanced Organic Chemistry, March, 4th Ed., John Wiley and Sons, New York, NY, 1992; Advanced Organic Chemistry, Carey and Sundberg, Vol. A and B, 3rd Ed., Plenum Press, Inc., New York, NY, 1990; Protective groups in Organic Synthesis, Green and Wuts, 2nd Ed., John Wiley and Sons, New York, NY, 1991; Comprehensive Organic Transformations, Larock, VCH Publishers, Inc., New York, NY, 1988; Handbook of Heterocyclic Chemistry, Katritzky and Pozharskii, 2nd Ed., Pergamon, New York, NY, 2000 and references cited therein. The starting materials for the present compounds may be prepared using standard synthetic transformations of chemical precursors that are readily available from commercial sources, including Aldrich Chemical Co. (Milwaukee, WI); Sigma Chemical Co. (St. Louis, MO); Lancaster Synthesis (Windham, N.H.); Ryan Scientific (Columbia, S. C.); Maybridge (Cornwall, UK); Matrix Scientific (Columbia, S. C.); Arcos, (Pittsburgh, PA) and Trans World Chemicals (Rockville, MD).

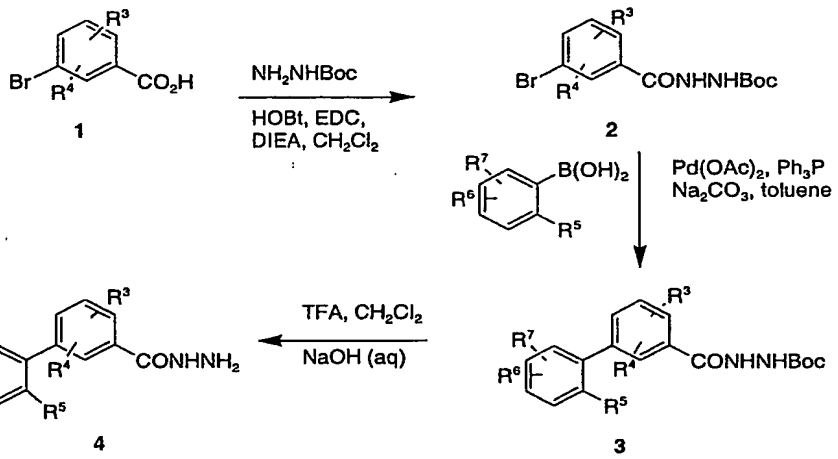
The procedures described herein for synthesizing the compounds may include one or more steps of protecting group manipulations and of purification, such as, recrystallization, distillation, column chromatography, flash chromatography, thin-layer chromatography (TLC), radial chromatography and high-pressure chromatography (HPLC). The products can be characterized using various techniques well known in the chemical arts, including proton and carbon-13 nuclear magnetic

resonance (^{1}H and ^{13}C NMR), infrared and ultraviolet spectroscopy (IR and UV), X-ray crystallography, elemental analysis and HPLC and mass spectrometry (LC-MS). Methods of protecting group manipulation, purification, structure identification and quantification are well known to one skilled in the art of chemical synthesis.

It is understood that the functional groups present in compounds described in the Schemes below can be further manipulated, when appropriate, using the standard functional group transformation techniques available to those skilled in the art, to provide desired compounds described in this invention.

Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.

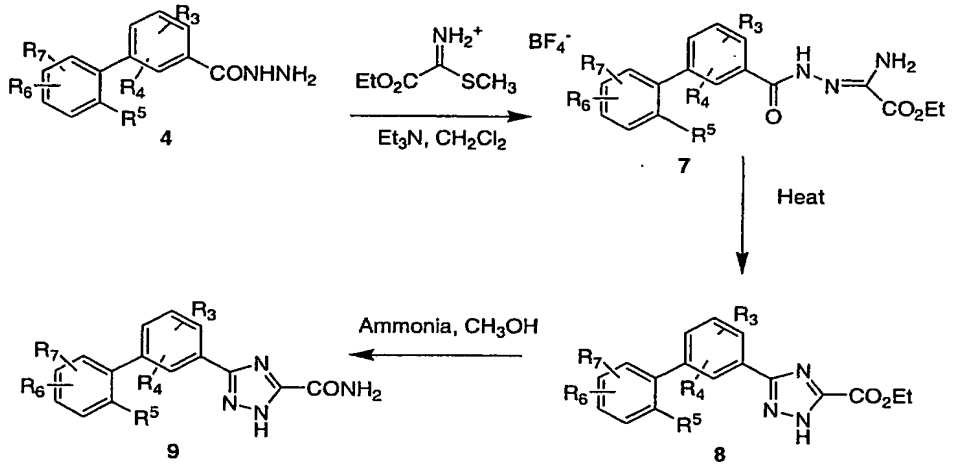
Scheme 1:



In one protocol, 3-bromobenzoic acid **1** is coupled with t-butyl carbazate by activation with HOBt (hydroxybenzotriazole) in the presence of a suitable carbodiimide such as EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide) and diisopropylethylamine (DIEA) in dichloromethane or THF to give the protected hydrazide **2**. There are numerous other suitable methods to activate carboxylic acids for coupling formation (see March J. "Advanced Organic Chemistry", 5th ed., John Wiley & Sons, New York, pp. 506-512 (2001). Compound **2** can be converted to a variety of unsymmetrical biphenyl intermediates **3** by means of a variety of coupling reactions. One type is the Suzuki reaction wherein bromo, iodo, or triflate compound **2** is reacted with an aryl boronic acid in the presence of a palladium catalyst such as palladium acetate with triphenyl phosphine and aqueous sodium carbonate in a solvent

such as toluene and a co-solvent such as n-propanol. (see Suzuki , *et al.* Chem. Rev., 95, 2457, 1995). A variety of aryl boronic acids are commercially available or can be prepared conveniently from the corresponding aryl bromide or iodide by converting it to an organolithium derivative [Baldwin, J. E., *et al. Tetrahedron Lett.* 39, 707-710 (1998)], or a Grignard reagent followed by treatment with trialkylborate [Li, J. J. et al, *J. Med. Chem*, 38: 4570-4578(1995) and Piettre, S. R., *et al. J. Med Chem.* 40, 4208-4221 (1997)]. Aryl boronates can also be used as an alternative to aryl boronic acids in these Pd-catalyzed coupling reactions [Giroux, A. , *et al.*, *Tetrahedron Lett.*, 38, 3841(1997)]. The boronates can be easily prepared from the aryl bromides, iodides and trifluoromethane sulfonates using the method described by Murata, M., *et al.* [*J. Org. Chem.* 65: 164-168 (2000)]. The Boc protecting group of compound 3 is removed by standard conditions - trifluoroacetic acid in dichloromethane - to give the TFA salt of hydrazide 4 which can be desalted with aqueous NaOH solution.

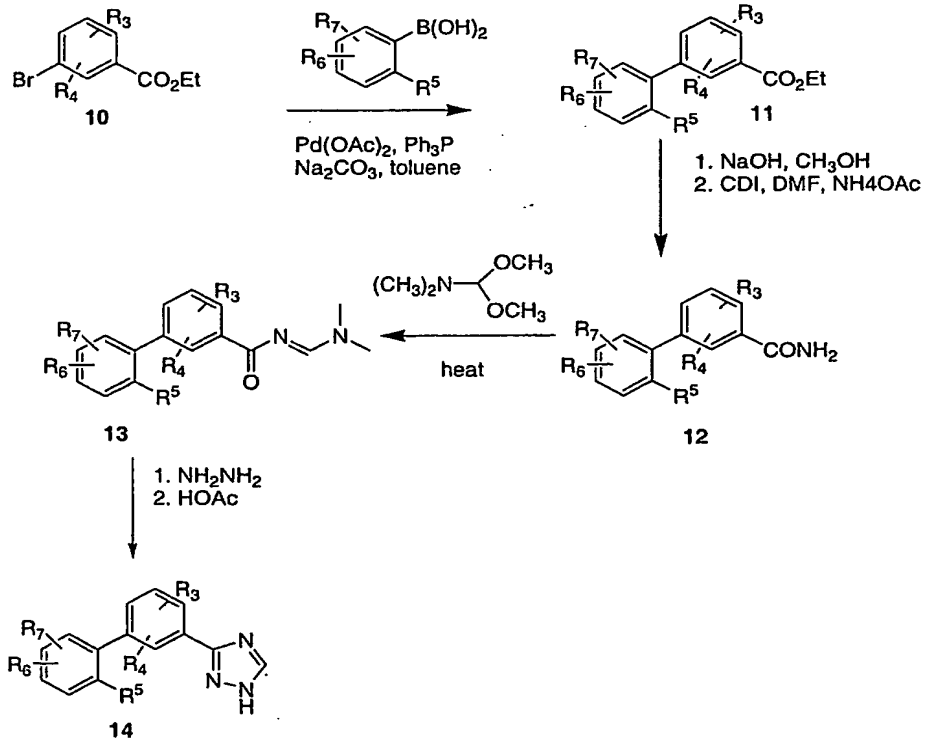
Scheme 2:



In Scheme 2, a method is described for preparing 5-biphenyl-3-substituted-1, 2, 4-triazole derivatives wherein the substitution can be esters, acids, amides, etc. (Catarzi , *et al. J. Med. Chem.*, 38, 2196-2201, 1995). Reaction of hydrazide 4 with carbethoxy-S-methyl-thioformimidium tetrafluoroborate and triethylamine in dichloromethane gives oxamidrazonate 7 which is cyclized to triazole ester 8. The reagent carbethoxy-S-methyl-thioformimidium tetrafluoroborate is prepared by reaction of ethyl-2-thiooxamate with trimethyl oxonium tetrafluoroborate (see Catarzi, *et al.* above) in dichloromethane. Ester 8 can be converted to an amide by heating it with the corresponding amine, in this case ammonia, in a solvent such as methanol. Ester 8 can be hydrolyzed to the corresponding acid

under standard conditions, and the resulting acid can be converted to an amide under a variety of conditions such as those described in Scheme 1. Additionally, ester 8 can be reduced to a primary alcohol with, for example, sodium borohydride ($NaBH_4$), to provide compounds of Formula (I) wherein R^1 is hydroxymethyl. Alternatively, ester 8 can be converted to a secondary alcohol by reaction with a mixture of lithium borohydride and a Grignard reagent in an aprotic solvent such as THF. Such primary or secondary alcohol derived from ester **8** can be further derivatized by a number of methods, including oxidation to a ketone by an oxidizing reagent such as a chromium-based reagent. Such alcohol can also be converted to a fluoride derivative by, for example, reaction with diethylaminosulfurtrifluoride (DAST) in dichlormethane at reduced temperatures.

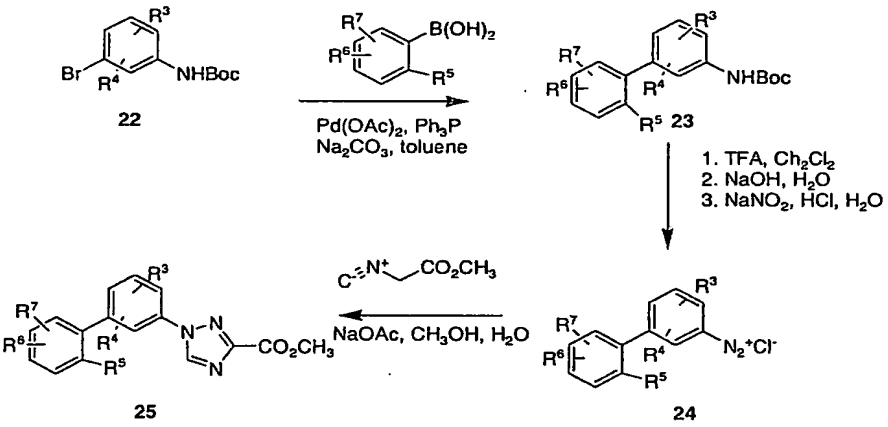
Scheme 3:



In Scheme 3, a method is described for preparing an unsubstituted 3-triazole ring system (Lin, *et al*, *J.Org. Chem.*, 44(23), 4160-4165, 1979). Ethyl-3-bromobenzoate **10** is reacted with an aryl boronic acid as described in Scheme 1 to give biphenylester **11.** The ester **11** provides a preformed biphenyl intermediate that can be further elaborated to compound 4 and related derivatives as described

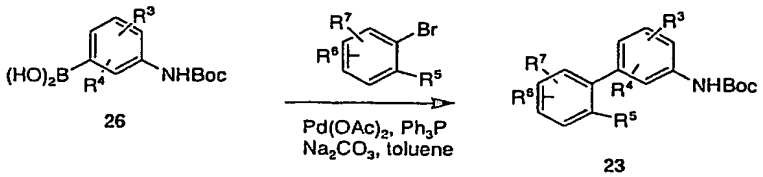
in earlier Schemes 1-2. In this Scheme 3, ester **11** is converted to amide **12** under standard conditions. Specifically, ester **11** is hydrolyzed to the corresponding acid which is then activated with carbonyldiimidazole (CDI) in DMF, followed by the addition of ammonia in the form of ammonium acetate to give amide **12**. Amide **12** in dimethylformamide dimethylacetal is heated to give intermediate **13** which, when heated with hydrazine in acetic acid, gives triazole **14**.

Scheme 4:



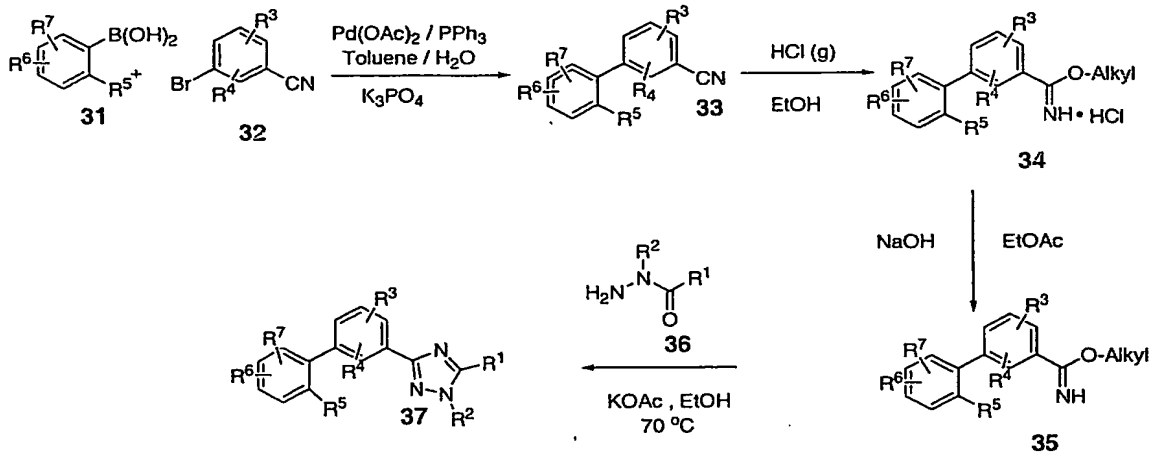
In a protocol to prepare 1-biphenyl-3-substituted-1,2,4-triazole derivatives, bromoaniline **22**, wherein the amino group is protected with a Boc group, and an arylboronic acid is converted to a variety of unsymmetrical biphenyl intermediates **23** as described in Scheme 1. The Boc protecting group of compound **23** is removed as described previously and converted to its diazonium salt **24** by standard reaction with sodium nitrite and HCl in water. Addition of compound **24** to a mixture of methylisocyanoacetate and sodium acetate in methanol and water gave the triazole ester **25**. The key intermediate **25** can be then converted to a variety of useful derivatives using the methods described in Schemes 1-3.

Scheme 5:



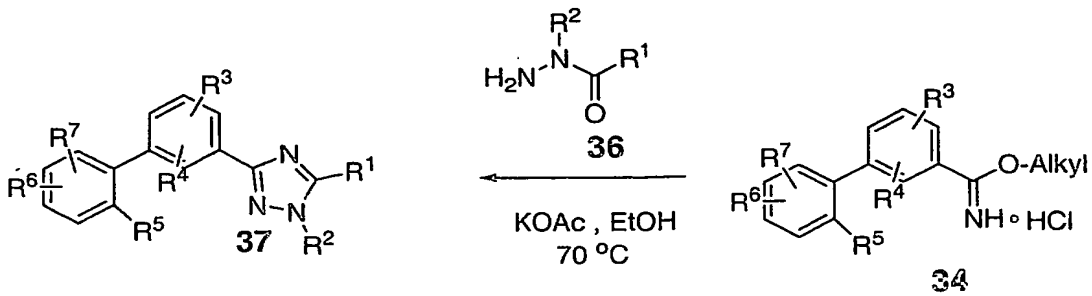
In a variation to the protocols described in Schemes 1, 3 and 4 above, the Boc-protected anline **26** containing a boronic acid group or boronate ester and an aryl bromide, iodide or triflate is converted to a variety of unsymmetrical biphenyl intermediates **23** as described in Scheme 1.

Scheme 6:



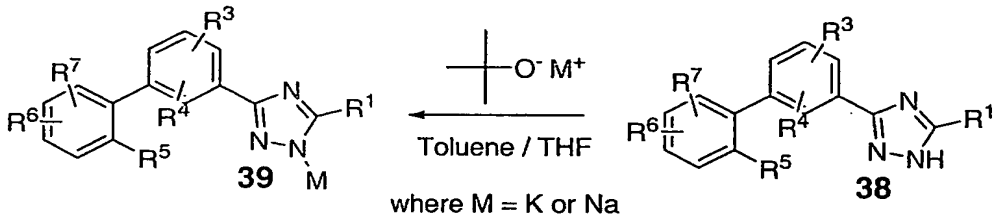
In accordance with Scheme 6, **31** and **32** can be converted to a biphenyl intermediate **33** by using, for example, a Suzuki-Miyaura coupling reaction with a palladium acetate/triphenyl phosphine catalyst system. The biphenyl intermediate **33** can be converted to imidate HCl salt **34** under standard Pinner conditions using, for example, a concentrated hydrochloric acid ethanolic solution. The imidate **34** can be converted to triazole **37** by free basing using a biphasic mixture such as EtOAc and NaOH to give ethyl imidate **35**, followed by treatment with oxamic hydrazide **36**, an alcoholic solvent such as ethanol and any one of many appropriate bases, including a metal acetate base such as potassium acetate, a tertiary amine base or a metal carbonate base, followed by heating.

Scheme 7:



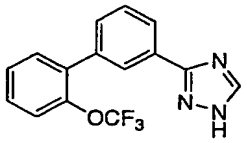
In a variation to Scheme 6, the imidate **34** is converted to triazole **37** by direct addition of oxamic hydrazide **36**, an alcoholic solvent such as ethanol and any one of many appropriate bases, including a metal acetate base such as potassium acetate, a tertiary amine base, or a metal carbonate base, followed by heating.

Scheme 8:



In accordance with Scheme 8, compounds of Formulas (I) or (II) wherein R^2 is H, **38**, can be converted by deprotonation with a metal alkoxide base such as potassium *tert*-butoxide or sodium *tert*-butoxide in an appropriate solvent/co-solvent mixture to yield a salt **39**.

EXAMPLE 1



3-[3-(2-Trifluoromethoxyphenyl)-phenyl]-1,2,4-triazole

Step A: 2-Trifluoromethoxyphenylboronic acid

To a stirred solution of 2 g (9.5 mmol) of 1-bromo-2-trifluoromethoxy benzene in 28 Ml of tetrahydrofuran (THF) at – 78°C, was carefully added a solution of 5.9 Ml of a 1.7 M solution of t-butyl lithium in hexanes (9.5 mmol). This reaction mixture was stirred at -78 °C for 45 min. To this reaction mixture at -78°C was added 2.58 Ml (11.1 mmol) of tri-isopropyl borate and the mixture was slowly warmed to room temperature (RT) over a period of 16 h. The reaction mixture was diluted with water and made basic with 2N NaOH solution. The reaction mixture was washed with EtOAc. The aqueous fraction was acidified with 2N HCl solution and stirred for 1 h at RT. The reaction mixture was

extracted with EtOAc and the organic fractions were washed with water, saturated NaCl solution (brine), dried over Na_2SO_4 and filtered. The filtrate was concentrated to give the title compound as a white solid. ^{1}HNMR ($CDCl_3$) (δ, ppm): 7.96 (dd, *J*= 7.2, 1.6 Hz, 1 H), 7.53 (ddd, *J* = 9.1, 7.3, 1.8 Hz, 1 H), 7.38 (td, *J* = 7.3, 0.7 Hz, 1 H), 7.28 (d, *J* = 8.2 Hz, 1 H), 5.25 (br s, 2H). MS (M+H): 206.9.

Step B: Ethyl-3-(2-Trifluoromethoxyphenyl)-benzoate

To a solution of 0.94 g (4.58 mmol) of ethyl-3-bromobenzoate in 14.5 Ml of toluene at RT was added 0.25 g (0.218 mmol) of tetrakis(triphenylphosphine) palladium(0), 0.94 g (4.58 mmol) of 2-trifluoromethoxyphenylboronic acid, 2.22 Ml (4.45 mmol) of 2M aqueous sodium carbonate solution and 7 Ml of ethanol. The reaction mixture was heated at reflux for 18 h. The reaction mixture was cooled and diluted with ethyl acetate and water. The organic fraction was separated and washed with saturated NaCl solution (brine), dried over $MgSO_4$, filtered and the filtrate was concentrated to an oil which was purified by chromatography (silica, 1%, 5%, 30% successively ethyl acetate: hexanes) to give the title compound. ^{1}H NMR (CD_3OD) (δ, ppm): 8.02 (s, 1H), 7.97 (dd, J = 7.8, 1.2 Hz, 1H), 7.60 (dd, J = 7.7, 1.3 Hz, 1H), 7.50-7.33 (m, 5H), 4.31(q, 2H), 1.31(t, 3H). Mass Spectrum (ESI) m/e (M+1): 311.2.

Step C: 3-(2-Trifluoromethoxyphenyl)-benzoic acid

A solution of 0.3 g (4.19 mmol) of ethyl-3-(2-trifluoromethoxyphenyl) –benzoate and 8.3 Ml (8.3 mmol) of a 1N solution of NaOH in 12.5 Ml of methanol was stirred 18 h at RT. The reaction mixture was concentrated and the Ph was adjusted to Ph=2 with 1 N HCl solution. The mixture was extracted with ethyl acetate (EtOAc) and the organic fraction was dried over $MgSO_4$, filtered and the filtrate was concentrated to give the title compound as a white solid that was used without further purification.

Step D: 3-(2-Trifluoromethoxyphenyl)-benzamide

To a solution of 0.94 g (3.36 mmol) of 3-(2-trifluoromethoxyphenyl)-benzoic acid in 17 Ml of DMF was added 0.55 g (3.36 mmol) of carbonyldiimidazole (CDI) and the reaction was stirred at RT for 4 h. To the reaction mixture was added 2.6 g (33.6 mmol) of ammonium acetate and the reaction mixture was stirred over night at RT. The reaction mixture was partitioned between ethyl acetate and water and the organic fraction was washed with brine, dried over $MgSO_4$, filtered and the filtrate was

concentrated. The residue was purified by chromatography (silica, 30%, 50% successively EtOAc: hexanes) to give the title compound. Mass Spectrum (ESI) m/e (M+1): 282.2.

Step E: 3-[3-(2-Trifluoromethoxyphenyl)-phenyl]-1,2,4-triazole

A solution of 0.137 g (0.48 mmol) of 3-(2-trifluoromethoxyphenyl)-benzamide in 1 Ml of N,N-dimethylformamide dimethyl acetal was heated at 120° C for 2 h at which time the reaction was concentrated *in vacuo*. To this material in 2.3 Ml of acetic acid was added 0.028 g (0.55 mmol) of hydrazine hydrate and the reaction mixture was heated at 90 ^{O}c for 2 h. The reaction mixture was then concentrated and partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic fraction was washed with brine, dried over $MgSO_4$, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, 30:1, 9:1, 3:1 successively CH_2Cl_2: acetone) to give the title compound. ^{1}H NMR (CD_3OD) (δ, ppm): 8.32 (s, 1H), 8.06 (s, 1H), 7.98 (m, 1H), 7.50 (m, 3H), 7.39(m, 3H).Mass Spectrum (ESI) m/e (M+1): 306.1.

EXAMPLE 2

3-[3-(2-(2,2,2-Trifluoroethoxyphenyl)-phenyl]-1,2,4-triazole

Step A: 2-(2,2,2-Trifluoroethoxy)phenyl bromide

A solution of 0.35 g (2 mmol) of 2-bromophenol, 0.63 g (3 mmol) of 2,2,2-trifluoroethyliodide, 0.55 g (4 mmol) of potassium carbonate in 2 mL of DMF was reacted at 150°C in a microwave system (Personal Chemistry, Smithcreator) for 30 min. After cooling to RT, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic fraction was dried over $MgSO_4$, filtered and the filtrate was concentrated. The residue was purified by chromatography (5%, 10% successively EtOAc: hexanes) to give the title compound.

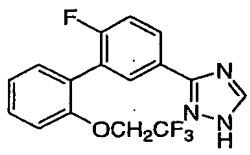
Step B: Ethyl 3-(2-(2,2,2-trifluoroethoxyphenyl)-benzoate

To a solution of 2.5 g (9.8 mmol) of 2-trifluoroethoxyphenyl bromide in 33 mL of toluene at RT was added 0.57 g (0.49 mmol) of tetrakis(triphenyl-phosphine) palladium(0), 0.2 g (10.3 mmol) of 3-ethoxycarbonylphenylboronic acid, 5.9 mL (11.8 mmol) of 2M aqueous sodium carbonate solution and 17 mL of ethanol. The reaction mixture was heated at reflux for 18 h. The reaction mixture was cooled and diluted with ethyl acetate and water. The organic fraction was separated and washed with saturated NaCl solution (brine), dried over $MgSO_4$, filtered and the filtrate was concentrated to an oil which was purified by chromatography (silica, 1%, 5%, 30% successively ethyl acetate: hexanes) to give the title compound. Mass Spectrum (ESI) m/e (M+1): 325.1.

Step C: 3-[3-(2-(2,2,2-Trifluoroethoxyphenyl)-phenyl]-1,2,4-triazole

The title compound can be prepared using procedures similar to that described in Example 1, Steps C – E.

EXAMPLE 3



3-[3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-(4-fluoro)phenyl]-1,2,4-triazole

Mass Spectrum (ESI) m/e (M+1): 338.0.

Step A: Methyl 3-((2-hydroxy)phenyl)-4-fluorobenzoate

To a solution of 2 g (8.45 mmol) of methyl-3-bromo-4-fluorobenzoate in 28 mL of toluene at RT was added 0.49 g (0.42 mmol) of tetrakis(triphenyl phosphine)palladium(0), 1.95 g (8.9 mmol) of 2-(4,4,5,5,-tetramethyl-1.3.2-dioxaborolan-2-yl)phenol, 5.1 mL (10.15 mmol) of 2M aqueous sodium carbonate solution and 14 mL of n-propanol. The reaction mixture was heated at reflux for 18 h. The reaction mixture was cooled and diluted with ethyl acetate and water. The organic fraction was separated and washed with saturated NaCl solution (brine), dried over $MgSO_4$, filtered and the filtrate was concentrated to an oil which was purified by chromatography (silica, 90:1, 30:1 successively CH_2Cl_2: acetone) to give the title compound. Mass Spectrum (ESI) m/e (M+1): 247.0.

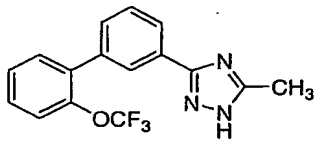
Step B: Methyl 3-((2-(2,2,2-trifluoroethoxy)phenyl)-4-fluorobenzoate

A mixture of 1.7 g (7.1 mmol) of methyl-3-((2-hydroxy)phenyl)-4-fluorobenzoate, 2.46 g (10.6 mmol) of 2,2,2,-trifluoroethyl trifluoromethanesulfonate and 3.45 g (10.6 mmol) of cesium carbonate in 35 mL of DMF was stirred at 60 °C for 18 h. The cooled reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic fractions were washed with water, brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated and purified by chromatography (silica, 5%, 30% successively EtOAc: hexanes) to give the title compound as a white solid. Mass Spectrum (ESI) m/e (M+1): 329.0.

Step C: 3-[3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-(4-fluoro)phenyl]-1,2,4- triazole

The title compound can be prepared using procedures similar to that described in Example 1, Steps C – E.

EXAMPLE 4



5-Methyl-3-[3-((2-trifluoromethoxy)phenyl)-phenyl]-1,2,4-triazole

Step A: 3-Bromophenylcarbonyl-(N-t-butoxycarbonyl)hydrazide

A solution of 1 g (4.97 mmol) of 3-bromobenzoic acid, 0.59 g (4.52 mmol) of t-butylcarbazate, 0.95 g (4.97 mmol) of EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), 0.67 g (4.97 mmol) of hydroxybenzotriazole (HOBt) and 3.15 mL (18.1 mmol) of diisopropylethylamine in 23 mL of CH_2Cl_2 was stirred at RT for 18 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 1N HCl solution, saturated $NaHCO_3$ solution and brine. The solution was dried over $MgSO_4$, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, 30:1, 9:1, 3:1 successively CH_2Cl_2:acetone) to give the title compound.
Mass Spectrum (ESI) m/e (M): 314.0, (M+2): 316.0

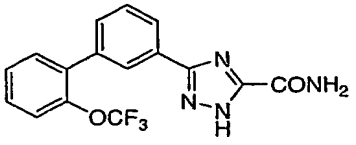
Step B: 3-((2-Trifluoromethoxy)phenyl)-phenylhydrazide

A solution of 0.22 g (1.07 mmol) of 2-trifluoromethoxyphenylboronic acid and 0.32 g (1.02 mmol) of 3-bromophenylcarbonyl-N-t-butoxycarbonylhydrazide in 5 mL of toluene and 2.5 mL of n-propanol was stirred for 30 min. To this reaction mixture was added 0.0007 g (0.003 mmol) of palladium acetate, 0.0024 g (0.009 mmol) of triphenylphosphine and 0.61 mL (1.2 mmol) of a 2M aqueous sodium carbonate solution and the reaction mixture was heated at reflux for 18 h. The reaction mixture was cooled and diluted with EtOAc and water. The organic fraction was dried over $MgSO_4$, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, 30:1, 9:1 successively, CH_2Cl_2: acetone) to give the protected hydrazide which was then dissolved in a mixture of 2.1 mL of TFA and 2.1 mL of CH_2Cl_2. The reaction mixture was stirred for 2 h whereupon it was concentrated, dissolved in CH_2Cl_2 and washed with 1N NaOH solution. The organic fraction was dried over $MgSO_4$, filtered and the filtrate was concentrated to give the tile compound as a white solid. Mass Spectrum (ESI) m/e (M+1): 297.1.

Step C: 5-Methyl-3-[3-((2-trifluoromethoxy)phenyl)-phenyl]-1,2,4-triazole

To a solution of 0.093 g (0.98 mmol) of acetamidine hydrochloride in 1.1 mL of ethanol was added 0.22 mL (0.98 mmol) of a 25% solution of sodium methoxide in methanol and the reaction mixture was stirred for 30 min. whereupon it was filtered. To the filtrate was added 0.19 g (0.66 mmol) of 3-((2-trifluoromethoxy) phenyl)-phenylhydrazide and the reaction mixture was stirred over night. The reaction mixture was concentrated and purified by chromatography (silica, 3%, 10%, 30% successively, methanol: CH_2Cl_2) to give a white solid. The white solid was heated (neat) to its melting temperature for 30 min. The reaction was cooled to RT, dissolved in CH_2Cl_2 and concentrated. The residue was purified by chromatography (silica, 3%, 10%, successively, methanol: CH_2Cl_2) to give the title compound as a white solid. ^1H NMR (CD_3OD) (δ,.ppm): 8.00 (s, 1H), 7.93 (m, 1H), 7.49 – 7.34 (m, 6H), 2.41(s, 3H). Mass Spectrum (ESI) m/e (M+1): 320.5.

EXAMPLE 5



3-[3-((2-Trifluoromethoxy)-phenyl)-phenyl]-1,2,4-triazole-5-carboxamide

Step A: Ethyl N^1-3-(2-trifluoromethoxy)-benzoyl-N^2-oxamidrazonate

To a solution of 0.45 g (1.54 mmol) of 3-(2-trifluoromethoxyphenyl)-phenylhydrazide (Example 4, Step B) in 20 mL of CH_2Cl_2 was added 0.54 g (2.3 mmol) of carbethoxy-S-methylthioformimidium tetrafluoroborate and 0.43 mL (3.08 mmol) of triethylamine and the reaction was stirred at refluxing temperatures for 4 hr. The reaction mixture was cooled to RT, washed with water, dried over Na_2SO_4, filtered and the filtrate was concentrated to a solid. Two mL of CH_2Cl_2 was added and the resulting solid product was recovered by filtration. Mass Spectrum (ESI) m/e (M+1): 396.1.

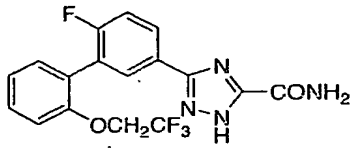
Step B: Ethyl 3-[3-((2-trifluoromethoxy)-phenyl)-phenyl]-1,2,4-triazole-5-carboxylate

The solid ethyl N^1-3-(2-trifluoromethoxy)-benzoyl-N^2-oxamidrazonate of Step A (0.25 g, 0.616 mmol) was heated in an oil bath above its melting point for 20 min. After cooling to RT, the residue was dissolved in CH_2Cl_2 and concentrated to give a yellow solid. It was purified by chromatography (silica, 10%, 30%, 50% successively, EtOAc: hexanes) to give a white solid. Mass Spectrum (ESI) m/e (M+1): 378.1.

Step C: 3-[3-((2-Trifluoromethoxy)-phenyl)-phenyl]-1,2,4-triazole-5-carboxamide

A solution of 0.13 g (0.34 mmol) of 5-ethyl-3-[3-((2-trifluoromethoxy)phenyl)-phenyl]-1,2,4-triazole-5-carboxylate (from Step B) in 2 mL of methanol in a tube was saturated with ammonia. The tube was sealed and the reaction mixture was heated at 60 °C overnight. The reaction mixture was then concentrated and the residue was purified by chromatography (silica, 3%, 10%, 20% successively methanol: CH_2Cl_2) to give the title compound. ^{1}H NMR (CD_3OD) (δ, ppm): 8.10 (s, 1H), 8.02 (m, 1H), 7.54 – 7.36 (m, 6H). Mass Spectrum (ESI) m/e (M+1): 349.2.

EXAMPLE 6



3-[3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-4-fluorophenyl]-1,2,4-triazole-5-carboxamide

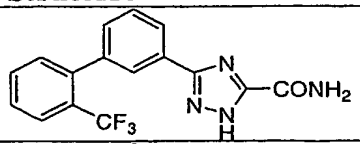
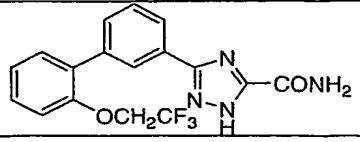
Step A: 3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-4-fluorobenzoic acid

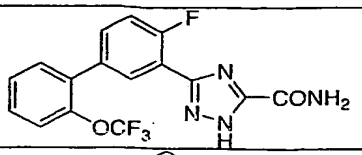
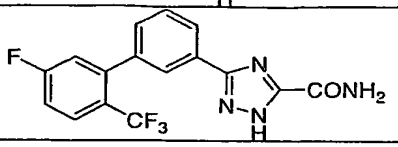
To a solution of 0.75 g (2.29 mol) of methyl 3-((2-(2,2,2-trifluoroethoxy)phenyl)-4-fluorobenzoate (Example 3, Step B) in 11.5 mL of a 3:1 mixture of THF: water was added 0.164 g (6.86 mmol) of LiOH and the reaction mixture was stirred at RT for 18 hr. The reaction mixture was concentrated and the pH was adjusted to pH = 2 with 1N HCl solution. The mixture was extracted with EtOAc and the combine organic fractions were washed with brine, dried over $MgSO_4$, filtered and the filtrate was concentrated to give the title compound which was used without further purification.

Step B: 3-[3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-4-fluorophenyl]-1,2,4-triazole-5-carboxamide

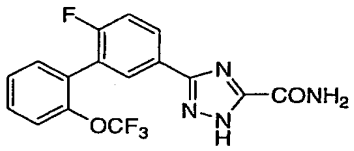
The title compound was prepared from 3-((2-trifluoroethoxy)phenyl)-4-fluorobenzoic acid according to procedures described in Example 4 Steps A&B and Example 4. ^1H NMR (CD_3OD) (δ, ppm): 8.02 (m, 2H), 7.99 (m, 1H), 7.39(m, 1H), 7.30 (m, 1H), 7.16(m, 2H), 4.45 (q, J = 8.5Hz, 2H).Mass Spectrum (ESI) m/e (M+1): 381.0.

The following Examples 7-10 were prepared according to procedures described in Examples 5 and 6.

Example No.	Structure	Mass Spectrum (M+1)
7		333.1
8		363.1

9		367.0
10		351.0

EXAMPLE 11



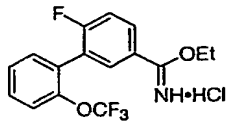
3-[3-((2-Trifluoromethoxy)-phenyl)-(4-fluoro)-phenyl]-1,2,4-triazole-5-carboxamide
Mass Spectrum (ESI) m/e (M+1): 367.0.

Step A: Preparation of 4-fluoro-3-(2-trifluoromethoxyphenyl)benzonitrile

3-bromo-4-fluorobenzonitrile (1.0 equivalent), 2-(trifluoromethoxy)benzeneboronic acid (1.25 equivalent), palladium acetate (0.005 equivalent) and triphenylphosphine (0.01 equivalent) were sequentially charged to a multi-necked flask. After purging the flask with nitrogen, toluene (5mL/gram of 3-bromo-4-fluorobenzonitrile) was added and the resulting slurry was stirred while bubbling nitrogen subsurface for about 20 minutes. In a separate flask, an aqueous potassium phosphate solution was prepared by dissolving solid potassium phosphate (2.0 equivalents) into water (2mL/gram of potassium phosphate). The resulting solution was de-oxygenated by bubbling nitrogen subsurface while stirring for about 30 minutes. The aqueous potassium phosphate solution was added to the toluene slurry and the reaction mixture was warmed to 60-65 °C by heating with steam. The progress of the reaction was monitored by HPLC and the reaction temperature was held between 63-69 °C. When 3-bromo-4-fluorobenzonitrile was consumed, heating was discontinued and the reaction mixture was cooled to RT using an ice bath. The aqueous layer was siphoned from the vessel and Ecosorb C-941 (0.5 gram/grams of 3-bromo-4-fluorobenzonitrile, commercially available from Graver Technologies, Glasgow, Delaware) was added to the reaction vessel. The resulting black slurry was stirred at RT for 15 hours. The carbon was removed by filtering the slurry through a pad of solka flok on a filter pot. The filter cake was

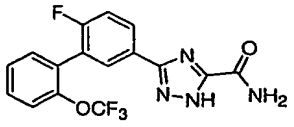
washed with toluene (4mL/gram of 3-bromo-4-fluorobenzonitrile). The combined filtrates were batch concentrated (40-50 °C) to provide the biaryl nitrile product as a thick, light-orange oil (94.0% yield).

Step B: Preparation of:



Absolute ethanol (1.8 mL/gram of biaryl nitrile) was charged to a round bottom flask. The stirred ethanol was chilled with an ice/acetone bath and gaseous hydrogen chloride was bubbled subsurface while the internal temperature was maintained less than 20 °C. Addition of HCl was monitored by proton titration using a Metrohm 808 Titrando (commercially available from Metrohm Ltd.) to determine HCl concentration of the ethanol solution. The addition was stopped after the concentration of HCl reached 38% (7.5 equivalents). The biaryl nitrile from step A (1.0 equivalent) was added as a neat oil to the chilled ethanolic HCl solution and the reaction solution was allowed to warm to RT while being stirred overnight (>15h). The reaction was deemed complete when assay by HPLC showed no presence of the starting biaryl nitrile. The resulting reaction was then diluted with toluene (8mL/gram of biaryl nitrile). To induce crystallization, the batch was solvent switched to toluene by co-distillation with ethanol (<35°C internal temperature) which azeotropically removed ethanol. This process was carried out until the ethanol content in the mother liquor was less than 1 mol% relative to toluene. This endpoint was determined by proton NMR in $CDCl_3$ of the mother liquor. The solids were isolated by filtration, washed with toluene (2.3mL/gram of biaryl nitrile). The white crystalline HCl salt of the ethyl imidate product was dried under a stream of nitrogen.

Step C: Preparation of:

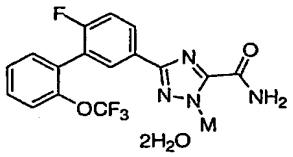


The imidate HCl salt from Step B (1.0 equivalent) and EtOAc (4mL/gram of imidate HCl salt) were added to a flask, followed by stirring to give a heterogeneous slurry. This slurry was cooled to 10°C followed by the slow addition of a solution of 5.0 N NaOH (3.3 equivalents). The rate of addition of the NaOH solution was periodically adjusted to maintain the reaction temperature below 15

°C. Once the addition of NaOH was complete, the biphasic reaction mixture was allowed to warm to ambient temperature at which point all of the solids had dissolved (ca. 30 min). Stirring was stopped and the two layers were allowed to separate. The bottom aqueous layer was removed and discarded. To the flask containing the organic layer was added water (2 mL/gram of HCl imidate salt) and the resulting biphasic mixture was stirred for 5 minutes. The layers were allowed to separate and the bottom aqueous layer was removed and discarded. This was followed by the addition of a 10% NaCl aqueous solution (2mL/gram of HCl imidate salt) to the flask. The resulting two layers were stirred for 5 minutes, and the bottom aqueous layer was removed and discarded. The top organic layer was transferred to a round bottom flask that was connected to a batch concentrator. A solvent switch from EtOAc to EtOH was then performed by removing the EtOAc by co-distillation with EtOH. Once the solvent switch was complete (< 3% EtOAc by ^{1}H NMR, imidate concentration approximately 185 mg/mL), the ethanolic solution containing the free base imidate was transferred to a new flask.

Oxamic hydrazide (1.1 equivalents) and potassium acetate (5.0 equivalents) were added to the ethanol solution containing the imidate from above. The resulting heterogeneous mixture was then heated to between 60-70 °C using a steam batch along with vigorous stirring. The reaction was monitored by HPLC analysis for conversion of the imidate to the desired triazole product. Once the reaction was complete, it was cooled to ambient temperature followed by the slow addition of water (4mL/gram of imidate HCl salt) to crystallize the desired product from the reaction. The desired product was then collected by vacuum filtration as an off-white solid (85% yield).

Step D: Preparation of:

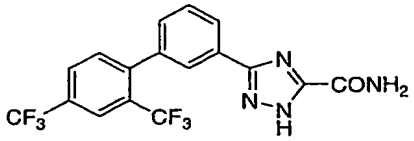


where M = K or Na

The triazole product of Step C (1.0 equivalents) was added to a reaction vessel, followed by the addition of toluene (5.3 mL/gram of triazole) and THF (1.7mL/gram of triazole). The resulting heterogeneous mixture was stirred at ambient temperature. To this slurry was added a solution of potassium tert-butoxide (1.1 equivalents). The rate of addition of the base was periodically adjusted to maintain the reaction temperature below 35 °C. As the addition proceeded, the reaction mixture became less heterogeneous. Once the addition of the base was complete, the now homogeneous light yellow solution was allowed to stir at ambient temperature for 30 min. At this point, water (2.5 equivalents) was

slowly added (ca. 10 min) to the batch with no noticeable exotherm. After about about 15 min, the reaction became increasingly cloudy and the batch temperature slowly began to rise. Approximately 20 min after addition of water, solids began to form indicating the crystallization had begun. After about 30 min, the batch temperature had reached its maximum (24.9 °C). The heterogeneous batch was allowed to stir for an additional 30 minutes. The batch was filtered onto a filter pot using the mother liquor to obtain any residual solids in the reaction vessel. The wet cake was washed with fresh toluene (4mL/gram of triazole). The batch was transferred to a vacuum oven and dried at 45°C and 100 torr for 24 hours to provide the potassium salt dihydrate product as a white solid (95% yield).

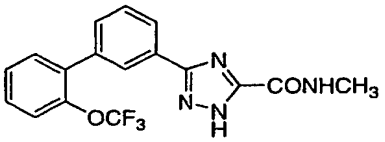
EXAMPLE 12



3-[3-((2,4-bis(trifluoromethyl)-phenyl)-phenyl]-1,2,4-triazole-5-carboxamide

Mass Spectrum (ESI) m/e (M+1): 401.0.

EXAMPLE 13

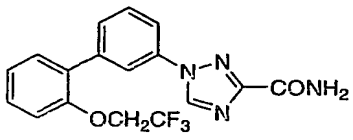


N-Methyl-3-[3-((2-trifluoromethoxy)-phenyl)-phenyl]-1,2,4-triazole-5-carboxamide

To a solution of 0.083 g (0.24 mmol) of 3-[3-((2-trifluoromethoxy)-phenyl)-phenyl]-1,2,4-triazole-5-carboxylic acid (made from ethyl 3-[3-((2-trifluoromethoxy)phenyl)-phenyl]-1,2,4-triazole-5-carboxylate of Example 5 according to procedures described in Example 6) in 1.2 mL of DMF at RT was added 0.038 g (0.24 mmol) of carbonyldiimidazole (CDI) and the reaction mixture was stirred for 3 hr. To the reaction mixture was added 1.2 mL (2.4 mmol) of a 2M solution of methylamine in THF and the reaction mixture was stirred overnight at RT. The reaction mixture was concentrated and partitioned between EtOAc and water. The aqueous fraction was extracted with EtOAc and the combined organic fractions were washed with water and brine, dried over $MgSO_4$, filtered and the filtrate

was concentrated. The residue was purified by chromatography (silica, 30%, 50% successively EtOAc: hexanes) to give the title compound as a foamy white solid. Mass Spectrum (ESI) m/e Mass Spectrum (ESI) m/e (M+1): 363.0.

EXAMPLE 14



1-[3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-phenyl]-1,2,4-triazole-3-carboxamide

Step A: 3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-aniline

To a solution of 1.0 g (3.93 mmol) of 2-(2,2,2-trifluoroethoxy)phenyl bromide (Example 2, Step A) in 39 mL of toluene was added 0.136 g (0.118 mmol) of tetrakis(triphenylphosphine)palladium(0), 0.56 g (4.31 mol) of 3-aminophenylboronic acid, 47 mL (94.1 mmol) of a 2M solution of sodium carbonate and 8 mL of ethanol and the reaction mixture was heated at 90 °C for 22 hr. The reaction mixture was cooled to RT, and partitioned between water and EtOAc. The aqueous fraction was extracted with EtOAc nd the combined organic fractions were washed with water and brine and dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, 4:1 hexanes: EtOAc) to give the title compound. Mass Spectrum (ESI) m/e M+1 268.1.

Step B: Methyl 1-[3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-phenyl]-1,2,4-triazole-3-carboxylate

To a solution of 0.923 g (3.45 mmol) of 3-((2-trifluoroethoxy)-phenyl)aniline in 6 mL of a 1N solution of HCl at 0 °C was added 0.238 g (3.45 mmol) of sodium nitrite and 1 mL of water and the reaction mixture was stirred for 20 min. to give the diazonium salt solution.

To a solution of 0.27 g (2.76 mmol) of methylisocyanoacetate in 15 mL of methanol and 2 mL of water at 0° C was added 1.8 g (22.08 mmol) of sodium acetate. To this reaction mixture was added dropwise the diazonium salt solution and the reaction mixture was stirred at 0° C for 1 h. The reaction mixture was then diluted with methanol and concentrated. The residue was diluted with EtOAc and 0.5N HCl solution. The aqueous layer was extracted with EtOAc and the combined organic

fractions were washed with 5% $NaHCO_3$ solution, brine, dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, 1:1 EtOAc: hexanes) to give the title compound. Mass Spectrum (ESI) m/e M+1 378.1.

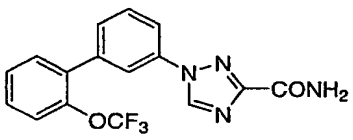
Step C: 1-[3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-phenyl]-1,2,4-triazole-3-carboxylic acid

A solution of 0.29 g (0.769 mmol) of methyl-1-[3-((2-trifluoroethoxy)-phenyl)-phenyl]-1,2,4-triazole-3-carboxylate and 2.2 mL (2.2 mmol) of a 1M solution of NaOH in water was stirred for 18 hr at RT. The reaction mixture was concentrated. The residue was diluted with water and the pH was adjusted to 2-4 with 1N HCl solution. The mixture was extracted with EtOAc and the combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated to give the title compound. Mass Spectrum (ESI) m/e M+1 363.9.

Step D: 1-[3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-phenyl]-1,2,4-triazole-3-carboxamide

To a solution of 0.225 g (0.619 mmol) of 1-[3-((2-trifluoroethoxy) phenyl)-phenyl]-1,2,4-triazole-3-carboxylic acid in 3.1 mL of DMF was added 0.1 g (0.19 mmol) of CDI and the reaction mixture was stirred at RT for 4 hr. To the reaction mixture was added 0.477 g (6.19 mmol) of ammonium acetate and the reaction mixture was stirred for 19 hr. The reaction mixture was diluted with water and EtOAc and the aqueous layer was extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica,1:1 EtOAc: hexanes, 1% methanol: CH_2Cl_2, 10% methanol: CH_2Cl_2) to give the title compound. Mass Spectrum (ESI) m/e M+1 363.1.

EXAMPLE 15



1-[3-((2-Trifluoromethoxy)-phenyl)-phenyl]-1,2,4-triazole-3-carboxamide

Step A: 1-N-t-butoxycarbonylamino-3-bromobenzene

A solution of 10 g (58.13 mmol) of 3-bromoaniline and 15.2 g (69.75 mmol) of Boc_2O in 300 mL of toluene was heated overnight at 70 °C. The reaction mixture was concentrated and diluted with EtOAc and 0.5N HCl solution. The organic fraction was washed with 0.5N HCl solution and brine. It was dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by chromatography (hexanes, 9:1 hexanes: EtOAc successively) to give the title compound.

Step B: 1-N-t-butoxycarbonyl-3-((2-Trifluoromethoxy)-phenyl) niline

1-N-t-Butoxycarbonylamino-3-bromobenzene was coupled with 2-trifluromethoxyphenylboronic acid according to procedures described in Example 14, Step A.

Step C: 3-((2-Trifluoromethoxy)-phenyl)aniline

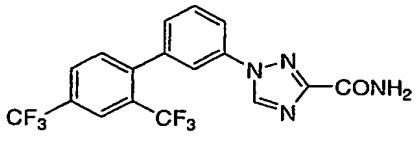
A solution of 0.977 g (2.77 mmol) of 1-N-t-butoxycarbonyl-3-((2-trifluoromethoxy)-phenyl)aniline in 7 mL of TFA and 7 mL of CH_2Cl_2 was stirred at RT for 1 hr. The reaction mixture was concentrated and the residue was diluted with 1N NaOH solution and EtOAc. The organic fraction was washed with 1N NaOH solution and brine, dried over Na_2SO_4 filtered and the filtrate was concentrated to give the title compound. Mass Spectrum (ESI) m/e M+1 254.1.

Step D: 1-[3-((2-Trifluoromethoxy)phenyl)-phenyl]-1,2,4-triazole-3-carboxamide

The title compound was prepared from 3-((2-trifluoro-methoxy)phenyl)aniline according to procedures described in Example 14. Mass Spectrum (ESI) m/e M+1 349.1.

The following Examples 16-17 were prepared according to the procedures described in Examples 14 or 15.

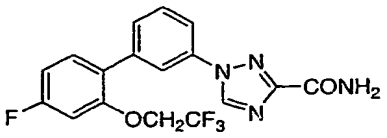
EXAMPLE 16



1-[3-((2,4-bis-trifluoromethyl)phenyl)-phenyl]-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e M+1 401.1.

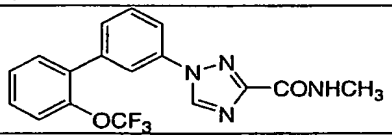
EXAMPLE 17



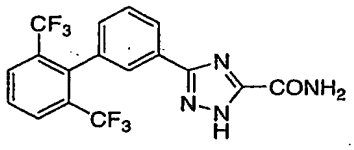
1-[3-((2-(2,2,2-Trifluoroethoxy-4-fluoro)phenyl)-phenyl]-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e M+1 381.2.

The following Example 18 was prepared according to procedures described in Example 13.

Example No.	Structure	Mass Spectrum (M+1)
18		363.1

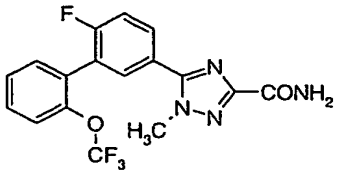
EXAMPLE 19



3-[3-((2,6-Bis-trifluoromethyl)-phenyl)-phenyl]-1,2,4-triazole-5-carboxamide

The titled compound is prepared using procedures described in Examples 5 and 6.

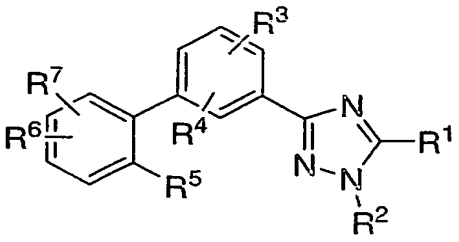
EXAMPLE 20



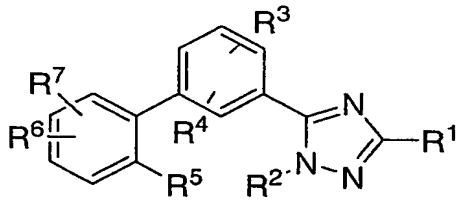
Mass Spectrum (ESI) m/e M+1 381

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I) or (II):



(I)



(II)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is

H;

C_1-C_6-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl,C_3-C_6-cycloalkyl, or C_1-C_4-alkyl-[C_3-C_6-cycloalkyl], any of which is optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, O-$CONR^aR^b$, NR^aR^b, $N(R^a)CONR^aR^b$, COO-(C_1-C_4)alkyl, COOH, CN, $CONR^aR^b$;

(a) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl;

(b) NR^aR^b, $-N(COR^a)R^b$, $-N(SO_2R^a)R^b$, $-N(R^a)CON(R^a)_2$, $-N(R^a)SO_2R^a$, $-N(OR^a)CONR^aR^b$, or $-N(R^a)SO_2N(R^a)_2$;

(c) $-CH(OR^a)R^a$, $-C(OR^b)CF_3$, $-CH(NHR^b)R^a$, $-C(=O)R^a$, $C(=O)CF_3$, $-SOCH_3$, $-SO_2CH_3$, $COOR^a$, CN, $CONR^aR^b$, $-COCONR^aR^b$, $-SO_2NR^aR^b$, $-CH_2O-SO_2NR^aR^b$, $SO_2N(R^a)OR^a$, $-C(=NH)NH_2$, $-CR^a=N-OR^a$, $CH=CHCONR^aR^b$;

(d) $-CONR^a(CH_2)_{0-2}C(R^a)(R^b)(CH_2)_{0-2}CONR^aR^b$;

(e) $-C(R^a)=C(R^b)-COOR^a$, or $-C(R^a)=C(R^b)-CONR^aR^b$;

R^a is

(a) H;

(b) C_1-C_4-alkyl, optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, $S(O)_{0-2}$-(C_1-C_4)alkyl, -$OCONH_2$, -OCONH(C_1-C_4alkyl), -OCON(C_1-C_4alkyl)(C_1-C_4alkyl), -OCONH(C_1-C_4alkyl-aryl), -OCON(C_1-C_4alkyl)(C_1-C_4alkyl-aryl), NH_2, NH(C_1-C_4alkyl), N(C_1-C_4alkyl)(C_1-C_4alkyl), NH(C_1-C_4alkyl-aryl), N(C_1-C_4alkyl)(C_1-C_4alkyl-aryl), $NHCONH_2$, NHCONH(C_1-C_4alkyl), NHCONH(C_1-C_4alkyl-aryl), -NHCON(C_1-C_4alkyl)(C_1-C_4alkyl), NHCON(C_1-C_4alkyl)(C_1-C_4alkyl-aryl), N(C_1-C_4alkyl)CON(C_1-C_4alkyl)(C_1-C_4alkyl), N(C_1-C_4alkyl)CON(C_1-C_4alkyl)(C_1-C_4alkyl-aryl), COO-(C_1-C_4-alkyl), COOH, CN, $CONH_2$, CONH(C_1-C_4alkyl), CON(C_1-C_4alkyl)(C_1-C_4alkyl);

(c) C_0-C_4-alkyl-(C_1-C_4)-perfluoroalkyl; or

(d) -C_1-C_4-alkyl-aryl, wherein aryl is phenyl, pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, triazolyl, pyrazolyl, thiazolyl, isoxazolyl, oxazolyl, or oxadiazolyl, any aryl of which is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) -NO_2, iv) –C(=O)(C_1-C_4alkyl), v) –O(C_1-C_4alkyl), vi) –N(C_1-C_4alkyl)(C_1-C_4alkyl), vii) -C_{1-10}alkyl, and viii) -C_{1-10}alkyl,wherein one or more of the alkyl carbons can be replaced by a -O-, -$S(O)_{1-2}$-, -O-C(O)-, -C(O)-O-, -C(O)-, -CH(OH)-, -C=C-, or -C≡C-;

R^b is

(a) H; or

(b) C_1-C_6-alkyl, optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, $S(O)_{0-2}$-(C_1-C_4)alkyl, -$OCONH_2$, -OCONH(C_1-C_4alkyl), NH_2, NH(C_1-C_4alkyl), N(C_1-C_4alkyl)(C_1-C_4alkyl), $NHCONH_2$, NHCONH(C_1-C_4alkyl), -NHCON(C_1-C_4alkyl)(C_1-C_4alkyl), COO-(C_1-C_4-alkyl), COOH, CN, or $CONH_2$;

R^2 is:

(a) H;

(b) -C_1-C_4-alkyl, -C_3-C_6-cycloalkyl or -C_1-C_4-alkyl-(C_3-C_6)-cycloalkyl, optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, $S(O)_{0-2}$-(C_1-C_4)alkyl, O-$CONR^aR^b$, NR^aR^b, $N(R^a)CONR^aR^b$, COO-(C_1-C_4)alkyl, COOH, CN, $CONR^aR^b$;

(c) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl;

(d) -C(=O)(R^a), -$CONR^aR^b$, -COO-(C_1-C_4)alkyl, - SO_2R^a, -$SO_2N(R^a)(R^b)$;

R^3 and R^4 each independently is:

(a) H;

(b) -C_1-C_6-alkyl, -C_2-C_6-alkenyl, -C_2-C_6-alkynyl or -C_3-C_6-cycloalkyl, any of which is optionally substituted with one or more of the following substituents: F, CF_3, -O-(C_1-C_4)alkyl, CN, -N(R^a)(R^b), -N(R^a)CO-(C_1-C_4)alkyl, $COOR^b$, CON(R^a)(R^b) or phenyl;

(c) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, or -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl; or

(d) CN, NH_2, NO_2, F, Cl, Br, I, OH, OCON(R^a)(R^b) O(C_1-C_4-alkyl)CONR^aR^b, -OSO_2N(R^a)(R^b), $COOR^b$, CON(R^a)(R^b), or aryl, wherein aryl is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) -NO_2, iv) –C(=O)(R^a), v) -OR^a, vi) -NR^aR^b, vii) -C_{0-4}alkyl-CO-OR^a, viii) -(C_{0-4}alkyl)-NH-CO-OR^a, ix) -(C_{0-4}alkyl)-CO-N(R^a)(R^b), x) -$S(O)_{0-2}R^a$, xi) -SO_2N(R^a)(R^b), xii) -$NR^aSO_2R^a$, xiii) -C_{1-10}alkyl, and xiv) -C_{1-10}alkyl,wherein one or more of the alkyl carbons can be replaced by a -NR^a-, - O-, -$S(O)_{1-2}$-, -O-C(O)-, -C(O)-O-, -C(O)-N(R^a)-, -N(R^a)-C(O)-, -N(R^a)-C(O)-N(R^a)-, -C(O)-, -CH(OH)-, -C=C-, or -C≡C; and

R^5, R^6 and R^7 each independently is:

(a) H;

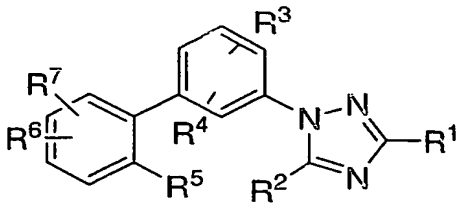
(b) C_1-C_6-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl or C_3-C_6-cycloalkyl, any of which is optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, OCON(R^a)(R^b), NR^aR^b, $COOR^a$, CN, $CONR^aR^b$, N(R^aR^b)$CONR^aR^b$;

(c) -O- C_1-C_6-alkyl, -O-C_3-C_6-cycloalkyl, -S-C_1-C_6-alkyl or -S-C_3-C_6-cycloalkyl, any of which is optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, NH_2, NH(C_1-C_4-alkyl), N(C_1-C_4-alkyl)$_2$, COOH , CN, $CONH_2$, CONH(C_1-C_4-alkyl), CONH(C_1-C_4-alkyl)$_2$, SO_2NH_2, SO_2NH(C_1-C_4-alkyl), tetrazolyl, triazolyl, imidazolyl, oxazolyl, oxadiazolyl, isooxazolyl, thiazolyl, furyl, thienyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyrazinyl, phenyl, piperidinyl, morpholinyl, pyrrolidinyl, or piperazinyl;

(d) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, or -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl;

(e) CN, N(R^a)(R^b), NO_2, F, Cl, Br, I, -OR^a, -SR^a, -OCON(R^a)(R^b), -OSO_2N(R^a)(R^b), $COOR^b$, CON(R^a)(R^b), -N(R^a)CON(R^a)(R^b), -N(R^a)SO_2N(R^a)(R^b), -C(OR^b)R^a, -C(OR^a)CF_3, -C(NHR^a)CF_3, -C(=O)R^a, C(=O)CF_3, -$SOCH_3$, -SO_2CH_3, -$NHSO_2$(C_{1-6}-alkyl), -$NHSO_2$-aryl, SO_2N(R^a)(R^b), -CH_2OSO_2N(R^a)(R^b), SO_2N(R^b)-OR^a, -C(=NH)NH_2, -CR_a=N-OR_a, CH=CH or aryl, wherein aryl is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) -NO_2, iv) –C(=O)(R^a), v) -OR^a, vi) -NR^aR^b, vii) -C_{0-4}alkyl-CO-OR^a, viii) -(C_{0-4}alkyl)-NH-CO-OR^a, ix) -(C_{0-4}alkyl)-CO-N(R^a)(R^b), x) -$S(O)_{0-2}R^a$, xi) -SO_2N(R^a)(R^b), xii) -$NR^aSO_2R^a$, xiii) -C_{1-10}alkyl, and xiv) -C_{1-10}alkyl, wherein one or more of the alkyl carbons can be replaced by a -NR^a-, - O-, -$S(O)_{1-2}$-, -O-C(O)-, -C(O)-O-, -C(O)-N(R^a)-, -N(R^a)-C(O)-, -N(R^a)-C(O)-N(R^a)-, -C(O)-, -CH(OH)-, -C=C-, or -C≡C.

2. A compound represented by Formula (III)



(III)

or a pharmaceutically acceptable salt thereof, wherein $R^1 - R^7$ each is as defined in Claim 1.

3. The compound of Claim 1 described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

R^5 is other than H, and all other variables are as previously defined.

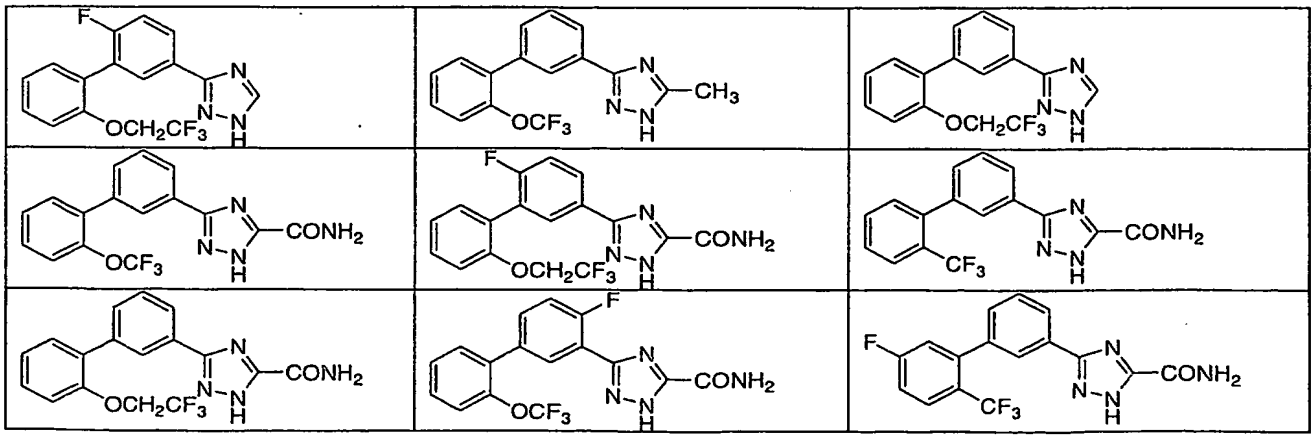
4. The compound of Claim 1 described by the chemical Formula (II), or a pharmaceutically acceptable salt thereof, wherein

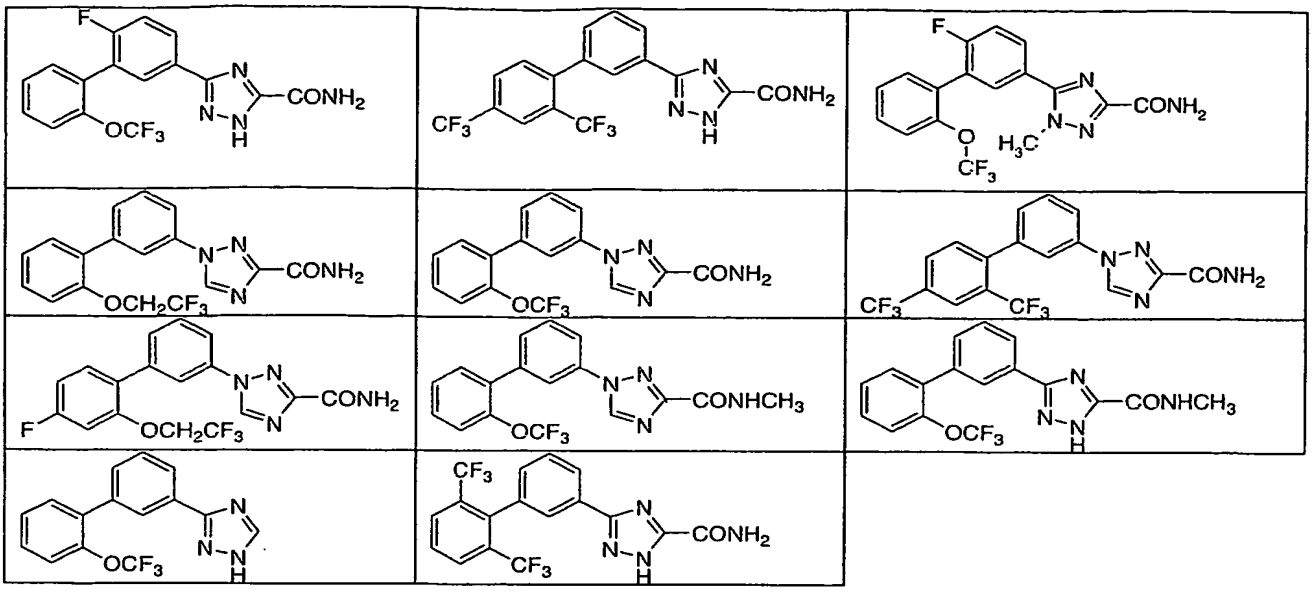
R^5 is other than H, and all other variables are as previously defined.

5. The compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^5 is other than H, and all other variables are as previously defined.

6. A compound represented by





7. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

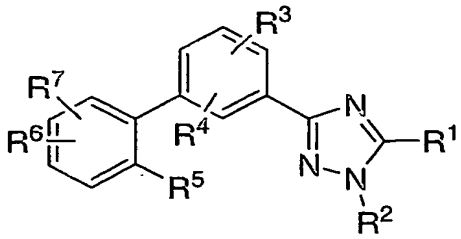
8. The pharmaceutical composition according to Claim 7, further comprising a second therapeutic agent.

9. A method of treatment or prevention of pain comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

10. Use of a compound of Claim 1 for preparing a medicament for treating or preventing pain or a pain associated disorder.

11. Use of a compound of Claim 2 for preparing a medicament for treating or preventing pain or a pain associated disorder.

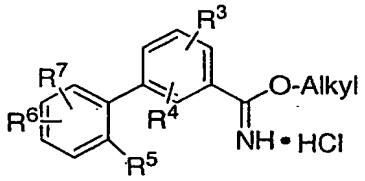
12. A process for making a compound of Formula (I):



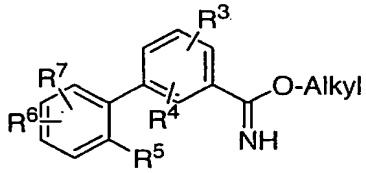
(I)

or a pharmaceutically acceptable salt thereof,

the process comprising reacting a compound of Formula **34** or **35**:

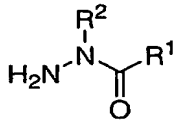


34



35

with a compound of Formula **36**:



36

wherein $R^1 - R^7$ each is as defined in Claim 1, in the presence of a base to yield a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

INTERNAT NAL SEARCH REPORT

International Application No
T/US2004/007830

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D249/08 C07D249/10 A61K31/4196 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 572 142 A (IHARA CHEMICAL IND CO ; KUMIAI CHEMICAL INDUSTRY CO (JP)) 1 December 1993 (1993-12-01) Table 11, Compounds No. 236-238 Table 16, Compound No. 407	1
X	DATABASE CAPLUS 'Online! AMERICAN CHEMICAL SOCIETY, COLUMBUS, OHIO, US; 12 May 1984 (1984-05-12), XP002291941 retrieved from STN Database accession no. 1973:72019 abstract -/--	2

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2004	24/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoepfner, W

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& M. A. KHAN ET AL.: "Synthesis of heterocyclic compounds. III. Aryl-1,2,4-triazoles" REVISTA LATINOAMERICANA DE QUIMICA, vol. 3, no. 3, 1972, pages 119-121, MONTERREY, MX	
X	WO 94/22852 A (SYNTEX INC) 13 October 1994 (1994-10-13) page 43, line 19 - line 34	2
A	WO 00/57877 A (COCENSYS INC ; NGUYEN PHONG (US); HOGENKAMP DERK J (US); UPASANI RAVIN) 5 October 2000 (2000-10-05) cited in the application page 1, line 12 - line 15 page 10, formula I page 31, Scheme 4 page 34, line 24 - line 28	1-12

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/US2004/007830

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/007830

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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